468792

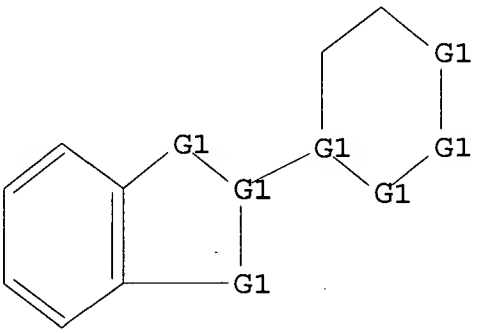
~~468472~~


```
=> d his

     (FILE 'HOME' ENTERED AT 10:59:12 ON 03 OCT 96)

     FILE 'REGISTRY' ENTERED AT 10:59:19 ON 03 OCT 96
L1               STRUCTURE UPLOADED
L2             0 S L1
L3         24168 S C4N-C6/EA AND C5N/EA
L4            22 S L1 SSS SAM  SUB=L3
L5          8843 S L3 AND 3/NR

=> d l1
'L1' HAS NO ANSWERS
L1               STR
```




```
G1 C,N


Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full sub=l5
FULL SUBSET SEARCH INITIATED 11:03:36
FULL SUBSET SCREEN SEARCH COMPLETED -   8547 TO ITERATE
100.0% PROCESSED    8547 ITERATIONS                          155 ANSWERS
SEARCH TIME: 00.00.16

L6           155 SEA SUB=L5 SSS FUL L1

=> save
ENTER L#, L# RANGE, ALL, OR (END):l6
ENTER NAME OR (END):a468792/a
ANSWER SET 'L6' HAS BEEN SAVED AS 'A468792/A'

=> file hcaplus
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	117.18	117.33

FILE 'HCAPLUS' ENTERED AT 11:04:39 ON 03 OCT 96

FILE COVERS 1967 - 3 Oct 1996 VOL 125 ISS 15
FILE LAST UPDATED: 3 Oct 1996 (961003/ED)

```
=> s ocular neovascular disease#
          5908 OCULAR
            93 NEOVASCULAR
        299704 DISEASE#
L7           1 OCULAR NEOVASCULAR DISEASE#
                 (OCULAR(W)NEOVASCULAR(W)DISEASE#)

=> s diabetic retinopathy
         21330 DIABETIC
          1105 RETINOPATHY
L8         569 DIABETIC RETINOPATHY
                 (DIABETIC(W)RETINOPATHY)

=> s corneal raft rejection#
          5023 CORNEAL
           421 RAFT
         12197 REJECTION#
L9           0 CORNEAL RAFT REJECTION#
                 (CORNEAL(W)RAFT(W)REJECTION#)

=> s neovascular glaucoma
            93 NEOVASCULAR
          2084 GLAUCOMA
L10          7 NEOVASCULAR GLAUCOMA
                 (NEOVASCULAR(W)GLAUCOMA)

=> s retrolental fibroplasia
            38 RETROLENTAL
           145 FIBROPLASIA
L11         36 RETROLENTAL FIBROPLASIA
                 (RETROLENTAL(W)FIBROPLASIA)
```

```
=> s epidemic keratoconjunctivitis
          1037 EPIDEMIC
           231 KERATOCONJUNCTIVITIS
L12          7 EPIDEMIC KERATOCONJUNCTIVITIS
                 (EPIDEMIC(W)KERATOCONJUNCTIVITIS)

=> s vitamin deficiency
         71681 VITAMIN
         86461 DEFICIENCY
L13        499 VITAMIN DEFICIENCY
                 (VITAMIN(W)DEFICIENCY)

=> s atopic keratitis
          1611 ATOPIC
           647 KERATITIS
L14          0 ATOPIC KERATITIS
                 (ATOPIC(W)KERATITIS)

=> s superior limbic keratitis
         58933 SUPERIOR
          3409 LIMBIC
           647 KERATITIS
L15          1 SUPERIOR LIMBIC KERATITIS
                 (SUPERIOR(W)LIMBIC(W)KERATITIS)

=> s pterygium keratitis sicca
            17 PTERYGIUM
           647 KERATITIS
           170 SICCA
L16          0 PTERYGIUM KERATITIS SICCA
                 (PTERYGIUM(W)KERATITIS(W)SICCA)

=> s sjogren#
L17        455 SJOGREN#

=> s acne rosacea
          1848 ACNE
            56 ROSACEA
L18          5 ACNE ROSACEA
                 (ACNE(W)ROSACEA)

=> s phylectenulosis
L19          0 PHYLECTENULOSIS
```

```
=> s syphilis
L20         523 SYPHILIS

=> s mycobacteria
L21        3176 MYCOBACTERIA

=> s lipid degeneration#
         145215 LIPID
          14887 DEGENERATION#
L22           18 LIPID DEGENERATION#
                 (LIPID(W)DEGENERATION#)

=> s ulcerr#
L23            0 ULCERR#

=> s ulcer#
L24       13660 ULCER#

=> s herpes simplex
          13794 HERPES
          13872 SIMPLEX
L25       10743 HERPES SIMPLEX
                 (HERPES(W)SIMPLEX)

=> s herpes zoster
          13794 HERPES
           1200 ZOSTER
L26          173 HERPES ZOSTER
                 (HERPES(W)ZOSTER)

=> s protozoa# infection#
           6095 PROTOZOA#
          99507 INFECTION#
L27          176 PROTOZOA# INFECTION#
                 (PROTOZOA#(W)INFECTION#)

=> s kaposi sarcoma
            354 KAPOSI
          18603 SARCOMA
L28          145 KAPOSI SARCOMA
                 (KAPOSI(W)SARCOMA)
```

```
=> s terriens marginal degeneration
             0 TERRIENS
         10799 MARGINAL
         14792 DEGENERATION
L29          0 TERRIENS MARGINAL DEGENERATION
                 (TERRIENS(W)MARGINAL(W)DEGENERATION)

=> s marginal keratolysis
         10799 MARGINAL
            11 KERATOLYSIS
L30          0 MARGINAL KERATOLYSIS
                 (MARGINAL(W)KERATOLYSIS)

=> s rheumatoid arthritus
          8078 RHEUMATOID
             1 ARTHRITUS
L31          0 RHEUMATOID ARTHRITUS
                 (RHEUMATOID(W)ARTHRITUS)

=> s rheumatoid arthritis
          8078 RHEUMATOID
         12611 ARTHRITIS
L32       5951 RHEUMATOID ARTHRITIS
                 (RHEUMATOID(W)ARTHRITIS)

=> s lupus
L33       4951 LUPUS

=> s polyarteritis
L34         61 POLYARTERITIS

=> s trauma#
L35       4876 TRAUMA#

=> s wegener## sarcoidosis
           142 WEGENER##
           576 SARCOIDOSIS
L36          0 WEGENER## SARCOIDOSIS
                 (WEGENER##(W)SARCOIDOSIS)

=> s scleritis
L37          9 SCLERITIS
```

```
=> s steven## johnson disease
          1092 STEVEN##
          3906 JOHNSON
        266712 DISEASE
L38          1 STEVEN## JOHNSON DISEASE
                 (STEVEN##(W)JOHNSON(W)DISEASE)

=> s periphigoid radial keratotomy
             0 PERIPHIGOID
         46806 RADIAL
            19 KERATOTOMY
L39          0 PERIPHIGOID RADIAL KERATOTOMY
                 (PERIPHIGOID(W)RADIAL(W)KERATOTOMY)

=> s corneal graph rejection#
          5023 CORNEAL
         11000 GRAPH
         12197 REJECTION#
L40          0 CORNEAL GRAPH REJECTION#
                 (CORNEAL(W)GRAPH(W)REJECTION#)

=> s sickle cell anemia
          2408 SICKLE
        926462 CELL
         12546 ANEMIA
L41       1552 SICKLE CELL ANEMIA
                 (SICKLE(W)CELL(W)ANEMIA)

=> s sarcoid
L42        111 SARCOID

=> s pseudoxanthoma elasticum
            28 PSEUDOXANTHOMA
            28 ELASTICUM
L43         28 PSEUDOXANTHOMA ELASTICUM
                 (PSEUDOXANTHOMA(W)ELASTICUM)

=> s pagets disease
            37 PAGETS
        266712 DISEASE
L44         35 PAGETS DISEASE
                 (PAGETS(W)DISEASE)
```

```
=> s vein occlusion
         28450 VEIN
         10683 OCCLUSION
L45        133 VEIN OCCLUSION
                 (VEIN(W)OCCLUSION)

=> s artery occlusion
         56701 ARTERY
         10683 OCCLUSION
L46       2501 ARTERY OCCLUSION
                 (ARTERY(W)OCCLUSION)

=> s carotid obstructive disease
          8807 CAROTID
          2173 OBSTRUCTIVE
        266712 DISEASE
L47          0 CAROTID OBSTRUCTIVE DISEASE
                 (CAROTID(W)OBSTRUCTIVE(W)DISEASE)

=> s uveitis
L48        581 UVEITIS

=> s vitritis
L49          2 VITRITIS

=> s lyme## disease
           601 LYME##
        266712 DISEASE
L50        443 LYME## DISEASE
                 (LYME##(W)DISEASE)

=> s eales disease
             6 EALES
        266712 DISEASE
L51          3 EALES DISEASE
                 (EALES(W)DISEASE)

=> s bechets disease
             0 BECHETS
        266712 DISEASE
L52          0 BECHETS DISEASE
                 (BECHETS(W)DISEASE)
```

```
=> s choroiditis
L53          4 CHOROIDITIS

=> s ocular histoplasmosis
          5908 OCULAR
           121 HISTOPLASMOSIS
L54          2 OCULAR HISTOPLASMOSIS
                 (OCULAR(W)HISTOPLASMOSIS)

=> s bests disease
            21 BESTS
        266712 DISEASE
L55          1 BESTS DISEASE
                 (BESTS(W)DISEASE)

=> s myopia
L56        107 MYOPIA

=> s optic pit#
         17348 OPTIC
         16766 PIT#
L57          2 OPTIC PIT#
                 (OPTIC(W)PIT#)

=> s stargarts disease
             0 STARGARTS
        266712 DISEASE
L58          0 STARGARTS DISEASE
                 (STARGARTS(W)DISEASE)

=> s pars planitis
          3677 PARS
             2 PLANITIS
L59          2 PARS PLANITIS
                 (PARS(W)PLANITIS)

=> s hyperviscosity syndrome#
            91 HYPERVISCOSITY
         37442 SYNDROME#
L60         26 HYPERVISCOSITY SYNDROME#
                 (HYPERVISCOSITY(W)SYNDROME#)

=> s toxoplasmosis
```

```
L61         427 TOXOPLASMOSIS

=> s rubeosis
L62           4 RUBEOSIS

=> s osteoarthritis
L63        1359 OSTEOARTHRITIS

=> s ulcerative colitis
           1391 ULCERATIVE
           1847 COLITIS
L64        1110 ULCERATIVE COLITIS
                  (ULCERATIVE(W)COLITIS)

=> s crohn## disease
            921 CROHN##
         266712 DISEASE
L65         305 CROHN## DISEASE
                  (CROHN##(W)DISEASE)

=> s bartonellosis
L66           9 BARTONELLOSIS

=> s hemanioma
L67           0 HEMANIOMA

=> s tumor#
L68      152603 TUMOR#

=> s cancer
L69       66783 CANCER

=> s metastasis
L70        8318 METASTASIS

=> s hemangioma#
L71         192 HEMANGIOMA#

=> s osler weber rendu
             22 OSLER
           1854 WEBER
             26 RENDU
L72           1 OSLER WEBER RENDU
```

(OSLER(W)WEBER(W)RENDU)

```
=> s rhabdomyosarcoma#
L73         885 RHABDOMYOSARCOMA#

=> s retinoblastoma
L74        1840 RETINOBLASTOMA

=> s sarcoma
L75       18603 SARCOMA

=> s neuroblastoma
L76        7212 NEUROBLASTOMA

=> s osteosarcoma
L77        2384 OSTEOSARCOMA

=> s leukemia#
L78       45504 LEUKEMIA#

=> s neoplast?
L79       22136 NEOPLAST?

=> s carcinoma
L80       46082 CARCINOMA

=> d his

     (FILE 'HOME' ENTERED AT 10:59:12 ON 03 OCT 96)

     FILE 'REGISTRY' ENTERED AT 10:59:19 ON 03 OCT 96
L1               STRUCTURE UPLOADED
L2             0 S L1
L3         24168 S C4N-C6/EA AND C5N/EA
L4            22 S L1 SSS SAM  SUB=L3
L5          8843 S L3 AND 3/NR
L6           155 S L1 SSS FULL  SUB=L5
                 SAVE L6 A468792/A

     FILE 'HCAPLUS' ENTERED AT 11:04:39 ON 03 OCT 96
L7             1 S OCULAR NEOVASCULAR DISEASE#
L8           569 S DIABETIC RETINOPATHY
L9             0 S CORNEAL RAFT REJECTION#
```

L10	7	S	NEOVASCULAR GLAUCOMA
L11	36	S	RETROLENTAL FIBROPLASIA
L12	7	S	EPIDEMIC KERATOCONJUNCTIVITIS
L13	499	S	VITAMIN DEFICIENCY
L14	0	S	ATOPIC KERATITIS
L15	1	S	SUPERIOR LIMBIC KERATITIS
L16	0	S	PTERYGIUM KERATITIS SICCA
L17	455	S	SJOGREN#
L18	5	S	ACNE ROSACEA
L19	0	S	PHYLECTENULOSIS
L20	523	S	SYPHILIS
L21	3176	S	MYCOBACTERIA
L22	18	S	LIPID DEGENERATION#
L23	0	S	ULCERR#
L24	13660	S	ULCER#
L25	10743	S	HERPES SIMPLEX
L26	173	S	HERPES ZOSTER
L27	176	S	PROTOZOA# INFECTION#
L28	145	S	KAPOSI SARCOMA
L29	0	S	TERRIENS MARGINAL DEGENERATION
L30	0	S	MARGINAL KERATOLYSIS
L31	0	S	RHEUMATOID ARTHRITUS
L32	5951	S	RHEUMATOID ARTHRITIS
L33	4951	S	LUPUS
L34	61	S	POLYARTERITIS
L35	4876	S	TRAUMA#
L36	0	S	WEGENER## SARCOIDOSIS
L37	9	S	SCLERITIS
L38	1	S	STEVEN## JOHNSON DISEASE
L39	0	S	PERIPHIGOID RADIAL KERATOTOMY
L40	0	S	CORNEAL GRAPH REJECTION#
L41	1552	S	SICKLE CELL ANEMIA
L42	111	S	SARCOID
L43	28	S	PSEUDOXANTHOMA ELASTICUM
L44	35	S	PAGETS DISEASE
L45	133	S	VEIN OCCLUSION
L46	2501	S	ARTERY OCCLUSION
L47	0	S	CAROTID OBSTRUCTIVE DISEASE
L48	581	S	UVEITIS
L49	2	S	VITRITIS
L50	443	S	LYME## DISEASE
L51	3	S	EALES DISEASE
L52	0	S	BECHETS DISEASE

```
L53           4 S CHOROIDITIS
L54           2 S OCULAR HISTOPLASMOSIS
L55           1 S BESTS DISEASE
L56         107 S MYOPIA
L57           2 S OPTIC PIT#
L58           0 S STARGARTS DISEASE
L59           2 S PARS PLANITIS
L60          26 S HYPERVISCOSITY SYNDROME#
L61         427 S TOXOPLASMOSIS
L62           4 S RUBEOSIS
L63        1359 S OSTEOARTHRITIS
L64        1110 S ULCERATIVE COLITIS
L65         305 S CROHN## DISEASE
L66           9 S BARTONELLOSIS
L67           0 S HEMANIOMA
L68      152603 S TUMOR#
L69       66783 S CANCER
L70        8318 S METASTASIS
L71         192 S HEMANGIOMA#
L72           1 S OSLER WEBER RENDU
L73         885 S RHABDOMYOSARCOMA#
L74        1840 S RETINOBLASTOMA
L75       18603 S SARCOMA
L76        7212 S NEUROBLASTOMA
L77        2384 S OSTEOSARCOMA
L78       45504 S LEUKEMIA#
L79       22136 S NEOPLAST?
L80       46082 S CARCINOMA

=> s l6
L81         502 L6

=> s l81 and l7-80
L82          84 L81 AND (L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14
                 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 O
                R L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR
                L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L3
                9 OR L40 OR L41 OR L42 OR L43 OR L44 OR L45 OR L46 OR L47
                OR L48 OR L49 OR L50 OR L51 OR L52 OR L53 OR L54 OR L55 OR
                 L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L
                64 OR L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71 OR L72
                 OR L73 OR L74 OR L75 OR L76 OR L77 OR L78 OR L79 OR L80)
```

```
=> s l82 and p/dt
       2135658 P/DT
L83          13 L82 AND P/DT

=> d ibib abs 1-13

L83  ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 1996 ACS
ACCESSION NUMBER:         1996:488756  HCAPLUS
DOCUMENT NUMBER:          125:123719
TITLE:                    Treatment of toxoplasmosis
INVENTOR(S):              El Kouni, Mahmoud H.; Guarcello, Vincent;
                          Naguib, Fardos N. M.
PATENT ASSIGNEE(S):       University of Alabama at Birmingham Research
                          Foundation, USA
SOURCE:                   PCT Int. Appl., 46 pp.
                          CODEN: PIXXD2

                          NUMBER                  DATE
                          --------------          ------
PATENT INFORMATION:       WO 9618398 A1           960620
DESIGNATED STATES:        W:  CA, JP
                          RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,
                          LU, MC, NL, PT, SE
APPLICATION INFORMATION:  WO 95-US16343           951214
PRIORITY APPLN. INFO.:    US 94-358195            941216
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
OTHER SOURCE(S):          MARPAT 125:123719
AB   Pharmaceutical compns. comprising purine analogs and uses for the
     compns. in treating parasite infections and other diseases or
     conditions are described.

L83  ANSWER 2 OF 13  HCAPLUS  COPYRIGHT 1996 ACS
ACCESSION NUMBER:         1996:326209  HCAPLUS
DOCUMENT NUMBER:          124:352750
TITLE:                    Pharmaceutical spray with systemic or local
                          action
INVENTOR(S):              Regenold, Juergen; Artmann, Carl; Roeding,
                          Joachim
PATENT ASSIGNEE(S):       Germany
SOURCE:                   Eur. Pat. Appl., 18 pp.
                          CODEN: EPXXDW
```

	NUMBER	DATE
PATENT INFORMATION:	EP 704206 A1	960403
DESIGNATED STATES:	R: AT, BE, CH, DE, ES, FR, GB, GR, IE, IT, LI, NL, PT	
APPLICATION INFORMATION:	EP 95-115315	950928
PRIORITY APPLN. INFO.:	DE 94-4434995	940930
	DE 94-4435010	940930
DOCUMENT TYPE:	Patent	
LANGUAGE:	German	

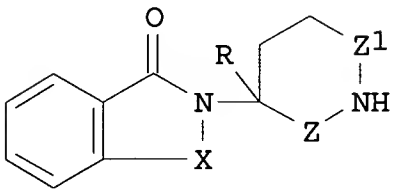
AB A pharmaceutical liq. compn. contg. .gtoreq.1 systemically and/or locally acting finely divided component is applied as a spray to the skin or mucous membranes, where evapn. of the liq. phase within <4 s results in a high concn. of the active agent(s) in the residue. If the compn. contains a gel-forming agent (e.g. a phospholipid mixt.), the residue takes the form of a concd. gel. This type of formulation is suitable for drugs which are usually administered orally or by injection, and can be more accurately dosed than other topical formulations such as creams and ointments; it also does not require use of excipients. Thus, a sprayable dispersion (pH 6.5) contained phospholipid gel-forming agent 10, EtOH 16, acemetacin 1, solid phosphate buffer 0.5, and H2O to 100 g.

L83 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER:	1996:181557 HCAPLUS
DOCUMENT NUMBER:	124:232439
TITLE:	Preparation of lactam immunomodulators and inhibitors of neo-angiogenesis
INVENTOR(S):	Boehlke, Horst; Finkam, Michael; Zimmer, Oswald; Schneider, Johannes; Wnendt, Stephan; Zwingenberger, Kai
PATENT ASSIGNEE(S):	Gruenenthal, GmbH, Germany
SOURCE:	Eur. Pat. Appl., 12 pp. CODEN: EPXXDW

	NUMBER	DATE
PATENT INFORMATION:	EP 688771 A1	951227
DESIGNATED STATES:	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE	
APPLICATION INFORMATION:	EP 95-109191	950614
PRIORITY APPLN. INFO.:	DE 94-4422237	940624
DOCUMENT TYPE:	Patent	

LANGUAGE: German
OTHER SOURCE(S): MARPAT 124:232439
GI



I

AB The title compds. (I; R = alkyl, PhCH2; X = S, Se, CH2; Z, Z1 = CH2, CO), which are useful as immunomodulations and inhibitors of neo-angiogenesis, are prepd. Thus, 2-(3-methyl-2-oxopiperidin-3-yl)benzo[d]isothiazol-3-one, prepd. from 3-amino-3-methyl-2-piperidone and o-chloromercaptobenzoyl chloride, demonstrated a 93 .+-. 9% inhibition of .alpha.-tumor necrosis factor at 50 .mu.g/mL, vs. 54 .+-. 7% for thalidomide.

L83 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:996589 HCAPLUS
DOCUMENT NUMBER: 124:45676
TITLE: Immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods
INVENTOR(S): Mak, Vivien H. W.
PATENT ASSIGNEE(S): De Novo Corp, USA
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2

	NUMBER	DATE
PATENT INFORMATION:	WO 9527510 A1	951019

DESIGNATED STATES:
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

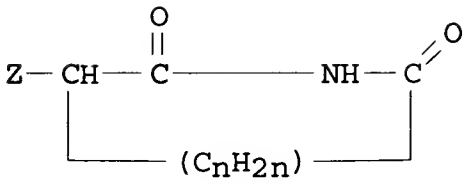
APPLICATION INFORMATION: WO 95-US4677 950411
PRIORITY APPLN. INFO.: US 94-225991 940412
US 94-271287 940706
US 95-400234 950303
DOCUMENT TYPE: Patent
LANGUAGE: English

AB Screening methods are provided for evaluating compds. capable of suppressing cytokine prodn. either in vitro or in vivo. The methods generally involve stimulating the prodn. of a cytokine in a cell, exposing a portion of the cells to a putative cytokine-modulating agent, and detg. subsequent levels of cytokine prodn. in the cells. Addnl., the present invention provides certain compds. identified by this method, as well as methods for treating conditions modulated by TNF. The methodol. of the invention may be used for e.g. prevention or redn. of transdermal drug delivery system-induced irritation and treatment of skin or systemic inflammatory conditions. Examples include e.g. inhibition of stimulated cytokine prodn. in human cells by a variety of drugs. Verapamil was effective in preventing the development of skin inflammatory responses in mice.

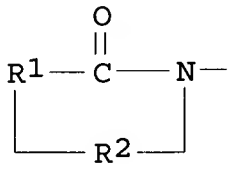
L83 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:964978 HCAPLUS
DOCUMENT NUMBER: 124:176936
TITLE: Prepn. of non-polypeptide imides as inhibitors of TNF.alpha.
INVENTOR(S): Muller, George W.
PATENT ASSIGNEE(S): Celgene Corporation, USA
SOURCE: U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 87,510, abandoned.
CODEN: USXXAM

	NUMBER	DATE
PATENT INFORMATION:	US 5463063 A	951031
APPLICATION INFORMATION:	US 93-140237	931020
PRIORITY APPLN. INFO.:	US 93-87510	930702

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE(S): CASREACT 124:176936; MARPAT 124:176936
GI



I



II

AB The present invention pertains to non-polypeptide imides, e.g., I wherein: Z = II, R3CONH, R4; R1 is the divalent residue of (i) pyridine, (ii) pyrrolidine, (iii) imidazole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with Ph or Ph substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms; R2 is CO or SO2; R3 is (i) Ph substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) naphthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, or (ix) indolyl; R4 is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thyronyl, tyrosyl, valyl, benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl; and n has a value of 1, 2, or 3, and their use as inhibitors of the action of TNF.alpha. (no data). Thus, e.g., a stirred mixt. of N-phthaloyl-L-glutamine (48.0 g, 174 mmol), carbonyldiimidazole (30.43 g, 188 mmoL), and 4-dimethylaminopyridine (0.105 g, 0.861 mmoL) in anhyd. THF (300 mL) was heated to reflux for 16 h; workup afforded 40.40 g (90%) of thalidomide.

L83 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:810892 HCAPLUS

DOCUMENT NUMBER: 123:237841
TITLE: Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions
INVENTOR(S): Piacquadio, Daniel J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM

	NUMBER	DATE
PATENT INFORMATION:	US 5443824 A	950822
APPLICATION INFORMATION:	US 94-212520	940314

DOCUMENT TYPE: Patent
LANGUAGE: English

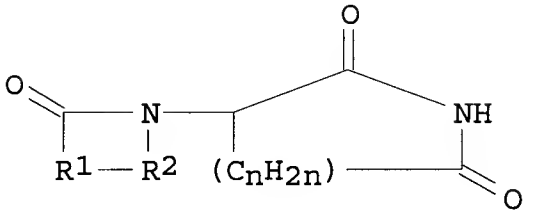
AB Surface wounds, ulcerations and lesions are treated with a solubilized topical compn. contg. as its active thalidomide (I) or a pro drug, analog or biol. active salt form thereof. A topical soln. contained azone 0.100, glycerin 0.020, propylene glycol 0.082, polypropylene glycol 0.042, 1,3-butanediol 0.038, polyethylene glycol E200 0.45, polysorbate 20 0.329, PEG E400 1.310, water 0.006, and alc. 0.062% wt./wt./I. Permeation of I through mouse skin was studied by Franz diffusion cells.

L83 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:797249 HCAPLUS
DOCUMENT NUMBER: 123:198617
TITLE: Imides as inhibitors of TNF alpha
INVENTOR(S): Muller, George W.
PATENT ASSIGNEE(S): Celgene Corp., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2

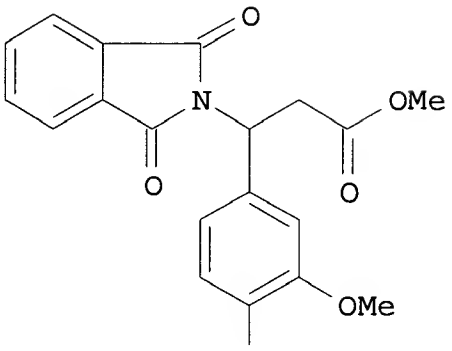
	NUMBER	DATE
PATENT INFORMATION:	WO 9501348 A2	950112
DESIGNATED STATES:	W: AU, CA, CZ, FI, HU, JP, KR, NZ, PL, RU, SK, UA, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE	
APPLICATION INFORMATION:	WO 94-US7411	940701
PRIORITY APPLN. INFO.:	US 93-87510	930702

DOCUMENT TYPE: Patent
LANGUAGE: English

OTHER SOURCE(S): MARPAT 123:198617
GI



I



II

AB A variety of cyclic imides and certain acyclic analogs and/or precursors are inhibitors of tumor necrosis factor .alpha. (no data) and can be used to combat cachexia, endotoxic shock, and retrovirus replication. One subgroup of the compds. is I [R1 = divalent residue of 3,4-pyridine, pyrrolidine, imidazole, naphthalene, thiophene, or C2-6 alkane (un)substituted by (un)substituted Ph; R2 = CO, SO2; n = 1-3]. A typical embodiment from a different subgroup is Me 3-phthalimido-3-(3,4-dimethoxyphenyl)propionate, i.e. II, which was prepd. from 3,4-(MeO)2C6H3CH(NH2)CH2CO2H by conversion to the Me ester hydrochloride with SOCl2 and MeOH (66%) and reaction of this with N-(carboethoxy)phthalimide in the presence of Na2CO3 in aq. MeCN (92%). A total of 93 synthetic examples and 6 formulations are given.

L83 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:756439 HCAPLUS
DOCUMENT NUMBER: 123:132879
TITLE: Method of treating intestinal disorders with anti-TNF agents
INVENTOR(S): Jackson, Graham Douglas Fischer
PATENT ASSIGNEE(S): Unisearch Ltd., Australia
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2

NUMBER DATE

	NUMBER	DATE
PATENT INFORMATION:	WO 9515179 A1	950608
DESIGNATED STATES:	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG	
APPLICATION INFORMATION:	WO 94-AU745	941201
PRIORITY APPLN. INFO.:	AU 93-2740	931201
	AU 94-8325	940921
DOCUMENT TYPE:	Patent	
LANGUAGE:	English	

AB The present invention provides a method of treating or preventing an intestinal disorder caused by an elevated level of TNF in the lumen of the intestine. The method involves administering to the subject an agent which reduces the action of the intralumenal TNF or reduces the prodn. or accumulation of intralumenal TNF. The agent may be any of a no. of known anti-TNF agents, however, it is preferred that the agent is an anti-TNF antibody. It is also preferred that the agent is administered directly into the intestine.

L83 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER:	1995:526821 HCAPLUS
DOCUMENT NUMBER:	122:274069
TITLE:	Use of tumor necrosis factor inhibitors together with antiviral agents, and therapeutic compositions thereof, against HIV infection
INVENTOR(S):	Andrulis, Peter J., Jr.; Angres, Issac
PATENT ASSIGNEE(S):	Andrulis Pharmaceuticals Corp., USA
SOURCE:	PCT Int. Appl., 12 pp. CODEN: PIXXD2

	NUMBER	DATE
PATENT INFORMATION:	WO 9504525 A2	950216
DESIGNATED STATES:	W: AU, CA, CN, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE	
APPLICATION INFORMATION:	WO 94-US8741	940803

PRIORITY APPLN. INFO.: US 93-101752 930804
DOCUMENT TYPE: Patent
LANGUAGE: English
AB A pharmaceutical compn. for treating HIV infection comprises (a) a tumor necrosis factor inhibitor (e.g. thalidomide, pentoxifylline, xanthine derivs.); (b) a compd. selected from a reverse transcriptase inhibitor (e.g. AZT, ddI, ddC), a protease inhibitor, a gene inhibitor, a myristoylation inhibitor, a cell-virus binding inhibitor, a LTR promoter site inhibitor, ribosome inactivators, a platelet aggregation inhibitor, and propylactic and therapeutic HIV vaccine, and (c) a pharmaceutical inert nontoxic carrier. A capsule formulation contains e.g. pentoxifylline and AZT.

L83 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:468706 HCAPLUS
DOCUMENT NUMBER: 122:222880
TITLE: Treatment of rheumatoid arthritis with thalidomide alone or in combination with other anti-inflammatory agents
INVENTOR(S): Andrulis, Peter J., Jr.
PATENT ASSIGNEE(S): Andrulis Pharmaceuticals Corp., USA
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2

	NUMBER	DATE
PATENT INFORMATION:	WO 9504533 A2	950216
DESIGNATED STATES:	W: AU, CA, CN, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE	
APPLICATION INFORMATION:	WO 94-US8742	940803
PRIORITY APPLN. INFO.:	US 93-101724	930804

DOCUMENT TYPE: Patent
LANGUAGE: English
AB A method for treating rheumatoid arthritis with thalidomide alone or in combination with anti-rheumatoid agents and/or with steroidal and/or nonsteroidal antiinflammatory drugs is described. Methods of treating rheumatoid arthritis with tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-inflammatory and/or anti-rheumatoid drugs are also described. Compns. contg. micronized thalidomide (particle size <1.0 .mu.) exhibit faster absorption

rates than previously known thalidomide formulations. Thus, thalidomide 100 mg, and ibuprofen 350 mg are mixed with lactose and triturated and filled into capsules.

L83 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:174382 HCAPLUS
DOCUMENT NUMBER: 122:151376
TITLE: Thalidomide compounds in methods and compositions for inhibition of angiogenesis
INVENTOR(S): D. Amato, Robert
PATENT ASSIGNEE(S): Children's Hospital Medical Center Corp., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2

	NUMBER	DATE
PATENT INFORMATION:	WO 9420085 A1	940915
DESIGNATED STATES:	W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG	
APPLICATION INFORMATION:	WO 94-US1971	940224
PRIORITY APPLN. INFO.:	US 93-25046	930301
	US 93-168817	931215

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE(S): MARPAT 122:151376

AB The present invention comprises a group of compds. that effectively inhibit angiogenesis. More specifically, thalidomide and various related compds. such as thalidomide precursors, analogs, metabolites and hydrolysis products have been shown to inhibit angiogenesis. Importantly, these compds. can be administered orally. EM-12 was tested in the rabbit cornea angiogenesis assay at 100 and 200mg/kg/day and showed 21% and 43% inhibition, resp.

L83 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1992:626313 HCAPLUS
DOCUMENT NUMBER: 117:226313
TITLE: Controlling abnormal concentration of tumor necrosis factor-.alpha.

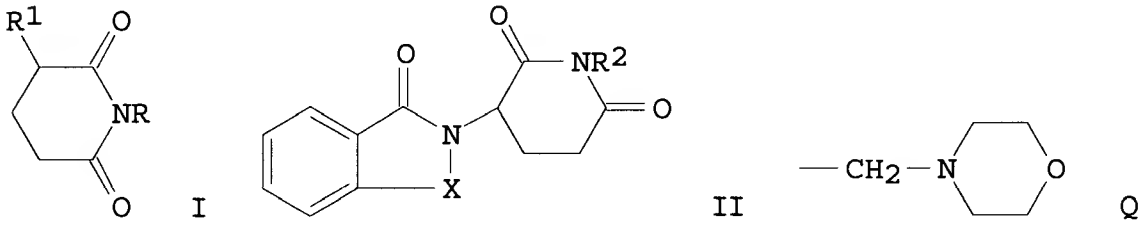
(TNF-.alpha.) in human tissues with phthalimido dioxopiperidines and related compounds

INVENTOR(S): Kaplan, Gilla; Sampaio, Elisabeth P.
PATENT ASSIGNEE(S): Rockefeller University, USA

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

	NUMBER	DATE
PATENT INFORMATION:	WO 9214455 A1	920903
DESIGNATED STATES:	W: AU, CA, JP RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE	
APPLICATION INFORMATION:	WO 92-US1207	920214
PRIORITY APPLN. INFO.:	US 91-655087	910214

DOCUMENT TYPE: Patent
LANGUAGE: English
GI



AB The dioxopiperidine derivs. I (R = H, alkyl, Ph, benzyl; R1 = phthalamide or succimido radical) and II (X = CH2, CO; R2 = H, Et, Ph, benzyl, CH2CH:CH2, Q) and II hydrolysis products, are drugs for treatment of the debilitating effects of toxic TNF-.alpha. levels in humans, such as in septic shock, cachexia and human immunodeficiency virus infection. Thalidomide (2 ng to 10 .mu.g/mL) decreased the tuberculin-stimulated prodn. of TNF-.alpha. in human monocytes in vitro. The prepn. of thalidomide and 3-phthalimido-2,6-dioxo-1-ethylpiperidine are given.

L83 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1976:577259 HCAPLUS
DOCUMENT NUMBER: 85:177259
TITLE: 1-Alkyl-4-phthalimide-2,6-piperidinediones

INVENTOR(S): Frankus, Ernst; Mueckter, Heinrich
PATENT ASSIGNEE(S): Chemie Gruenenthal G.m.b.H., Ger.
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX

	NUMBER	DATE
PATENT INFORMATION:	DE 2460304	760701
APPLICATION INFORMATION:	DE 74-2460304	741220

DOCUMENT TYPE: Patent
LANGUAGE: German
GI For diagram(s), see printed CA Issue.
AB Piperidinediones I (R = Me, Et, Pr), useful as antitumor agents, were prepd. Thus, 3-phthalimidoglutaric anhydride in dioxane was treated with NEt3, then PrNH2 to give 79% glutaramide II which was cyclized with Ac2O-SOCl2 to give 87% I (R = Pr). Aminopiperidinedione III refluxed with phthalic anhydride in PhMe contg. NEt3 or treated with Na2CO3 in H2O and then N-carbethoxyphthalimide gave I (R = Me). III was prepd. in 5 steps from 3-aminoglutaric acid and PhCH2O2CCl via PhCH2O2CNHCH(CH2CO2H)CH2CONHMe. Rats were each treated with 2 mg dimethylbenzanthracene i.v., then fed 0.25% I in feed after mammary tumors became evident. In 6 weeks, the av. no. of tumors of a group treated with I (R = Pr) decreased from 4.1 to 1.3 and the av. size from 821.9 mm2 to 162.4 mm2. In the control group, the no. increased from 4.1 to 7.1 and the size from 802.6 mm2 to 1778.3 mm2.

=> s l82 not l83
L84 71 L82 NOT L83

=> d ibib abs hitstr 1-71

L84 ANSWER 1 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:503303 HCAPLUS
DOCUMENT NUMBER: 125:185807
TITLE: Selection of novel analogs of thalidomide with enhanced tumor necrosis factor .alpha. inhibitory activity
AUTHOR(S): Corral, Laura G.; Muller, George W.; Moreira, Andre L.; Chen, Yuxi; Wu, Mingdan; Stirling, David; Kaplan, Gilla
CORPORATE SOURCE: Celgene Corporation, Warren, NJ, USA

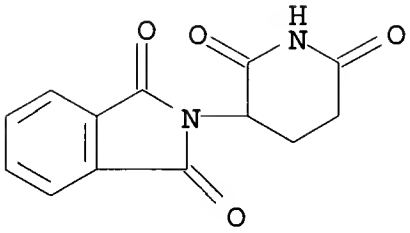
SOURCE: Mol. Med. (Cambridge, Mass.) (1996), 2(4), 506-515
CODEN: MOMEF3; ISSN: 1076-1551
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor necrosis factor .alpha. (TNF.alpha.) is thought to mediate both protective and detrimental manifestations of the inflammatory response. Recently, thalidomide (.alpha.-N-phthalimidoglutarimide) was shown to partially inhibit monocyte TNF.alpha. prodn. (by 50-70%) both in vivo and in vitro. More efficient inhibition of TNF.alpha. may, however, be necessary to rescue the host from more acute and extensive toxicities of TNF.alpha.-mediated inflammation. Three structural analogs of thalidomide were selected for study based on increased activity against TNF.alpha. prodn. The parent drug and the analogs were tested in vitro in human peripheral blood mononuclear cell cultures for their effects on lipopolysaccharide (LPS) induced cytokine protein and mRNA prodn. using ELISAs and Northern blot hybridization. The in vitro effects of the drugs were then confirmed in vivo in a mouse model of LPS induced lethality. The new compds. (2 esters and 1 amide) showed increased inhibition of TNF.alpha. prodn. by LPS-stimulated human monocytes, relative to the parent drug thalidomide. The analogs and the parent drug enhanced the prodn. of interleukin 10 (IL-10), but had little effect on IL-6 and IL-1.beta. protein and mRNA prodn. When tested in vivo, the amide analog protected 80% of LPS-treated mice against death from endotoxin induced shock. Thus, analogs of thalidomide designed to better inhibit TNF.alpha. prodn. in vitro have correspondingly greater efficacy in vivo. These findings may have therapeutic implication for the treatment of human diseases characterized by acute and extensive TNF.alpha. prodn. such as tuberculous meningitis or toxic shock.

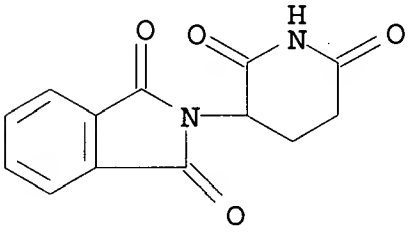
IT 50-35-1, Thalidomide 50-35-1D, Thalidomide, analogs
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(thalidomide analogs with enhanced tumor necrosis factor .alpha. inhibitory activity)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



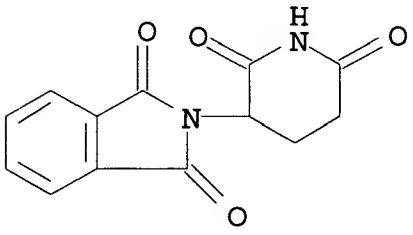
L84 ANSWER 2 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:490357 HCAPLUS
DOCUMENT NUMBER: 125:185255
TITLE: Thalidomide decreases the production of GM-CSF and TNF-.alpha. in the mixed epidermal cell-lymphocyte reaction
AUTHOR(S): Charue, Dominique; Chauvin, Emmanuelle; Duguet, Corinne; Revuz, Jean; Bagot, Martine
CORPORATE SOURCE: Department Dermatology, Paris XII University, Creteil, F-94010, Fr.
SOURCE: Eur. J. Dermatol. (1996), 6(5), 373-376
CODEN: EJDEE4; ISSN: 1167-1122
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thalidomide is an effective treatment for several dermatol. diseases. Recently, it has been used to treat Langerhans cell histiocytosis. The mechanism of this effect is poorly understood. In order to try to define the mechanism of action of thalidomide, we studied its effects (26 to 2600 ng/mL) on lymphocyte proliferation in mixed allogeneic reactions, on the induction of allogeneic cytotoxic activity, and on the prodn. of several cytokines in the

mixed epidermal cell-lymphocyte reaction, using an ELISA or a RIA test. Thalidomide and its solvent had no effect on either lymphocyte proliferation or the cytotoxic activity induced in mixed allogeneic reactions. In mixed epidermal cell-lymphocyte reactions, the prodn. of GM-CSF was decreased when either lymphoid cells or epidermal cells (EC) were preincubated with thalidomide. The prodn. of TNF-.alpha. and IL-6 was decreased only when lymphoid cells were preincubated with thalidomide. The prodn. of IL-1.beta. was not decreased when either EC or lymphoid cells were preincubated with thalidomide. In conclusion, thalidomide decreases the prodn. of several cytokines in MECLR, esp. GM-CSF and TNF-.alpha., which play a major role in the viability and function of Langerhans cells. This effect of thalidomide on the lymphocyte-epidermal cell interactions may, at least partly, explain the effect of thalidomide on Langerhans cell histiocytosis.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide effect on cytokine prodn. in mixed epidermal cell-lymphocyte reaction)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 3 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1996:452533 HCAPLUS

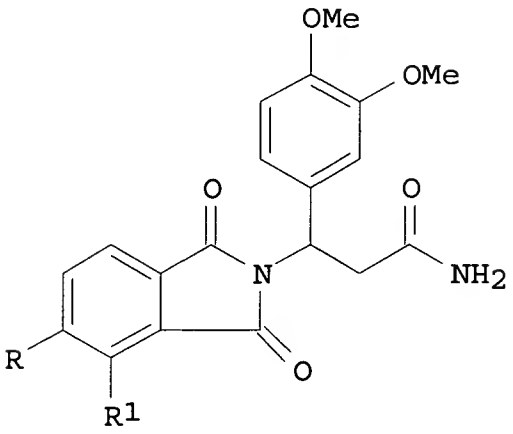
DOCUMENT NUMBER: 125:157753

TITLE: Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity

AUTHOR(S): Muller, George W.; Corral, Laura G.; Shire, Mary G.; Wang, Hua; Moreira, Andre; Kaplan, Gilla; Stirling, David I.

CORPORATE SOURCE: Celgene Corporation, Warren, NJ, 07059, USA
SOURCE: J. Med. Chem. (1996), 39(17), 3238-3240
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CJACS-IMAGE; CJACS

GI



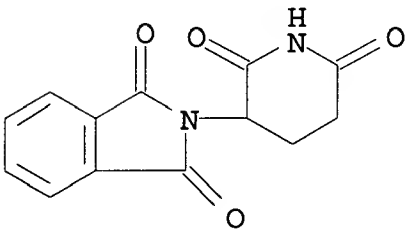
I

AB Thalidomide (.alpha.-N-phthalimidoglutarimide) has been shown to have a wide range of varied biol. activities, including the ability to inhibit tumor necrosis factor-.alpha. (TNF-.alpha.) prodn. and its accompanying inflammatory manifestations. The central role of TNF-.alpha. as a pro-inflammatory cytokine of the immune response suggests that the drug may have important therapeutic utility in a variety of diseases including acute and chronic infections, auto-immune disorders, and malignancies. To prep. a family of drugs with increased anti-TNF-.alpha. activity, a series of analogs of thalidomide was designed, synthesized, and tested for their ability to inhibit TNF-.alpha. release by peripheral blood mononuclear cells in vitro. A series of N-phthaloyl .beta.-amino-.beta.-aryl amides and esters was found to have increased activity in inhibiting TNF-.alpha. prodn. The more potent analogs reported here, compds. (I, R = H, R1 = NH2) and (II, R = NH2, R1 = H) are 400-500 times more active than thalidomide in inhibiting TNF-.alpha. prodn.

IT 50-35-1, Thalidomide 841-67-8, S-Thalidomide
2614-06-4, R-Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL

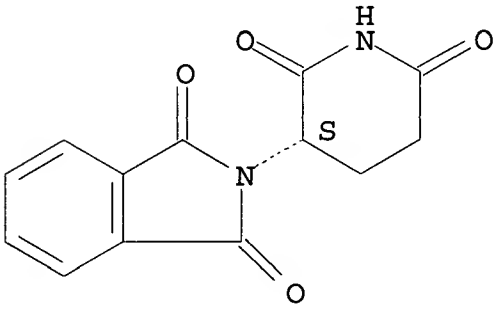
(Biological study)
(thalidomide analog prepn. for compds. with enhanced TNF-.alpha. inhibitory activity)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



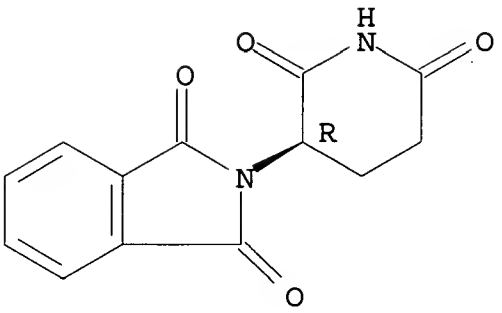
RN 841-67-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 2614-06-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

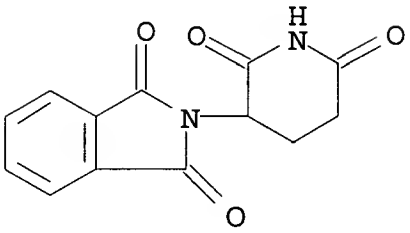


L84 ANSWER 4 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:447497 HCAPLUS
DOCUMENT NUMBER: 125:131756
TITLE: Thalidomide inhibits TNF response and increases survival following endotoxin injection in rats
AUTHOR(S): Schmidt, Hans; Rush, Benjamin; Simonian, Gregory; Murphy, Thomas; Hsieh, John; Condon, Michael
CORPORATE SOURCE: New Jersey Medical School, University Medicine and Dentistry New Jersey, Newark, NJ, 07103, USA
SOURCE: J. Surg. Res. (1996), 63(1), 143-146
CODEN: JSGRA2; ISSN: 0022-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

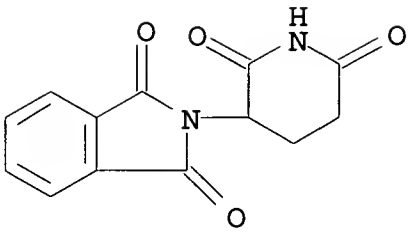
AB This study examd. the effect of thalidomide administration on survival and serum levels of tumor necrosis factor-.alpha. in a rat model of acute septic shock. Elevation of serum TNF occurred after endotoxin (Escherichia coli lipopolysaccharide) injection, with peak levels at 90 min. Thalidomide-treated rats had lower TNF levels than did untreated rats at all time points tested, with the inhibition being dose dependent. Survival of the treated rats exceeded that of untreated rats after 48 and 72 h. Thus, thalidomide administration leads to increased survival following acute endotoxemia, which may be due to the obsd. TNF inhibition.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor necrosis factor and survival in endotoxemia response to)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA

INDEX NAME)



L84 ANSWER 5 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:445095 HCAPLUS
DOCUMENT NUMBER: 125:104384
TITLE: Augmentation by phthalimides of phorbol ester-induced expression of tumor necrosis factor alpha message
AUTHOR(S): Azuma, Akihiko; Miyachi, Hiroyuki; Shibata, Yoshihiro; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. of Molecular and Cellular Biosciences, Univ. of Tokyo, Tokyo, 113, Japan
SOURCE: Biol. Pharm. Bull. (1996), 19(7), 1001-1003
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N(.alpha.)-phthalimidoglutarimide (thalidomide), 2-(2,6-diisopropylphenyl)-1H-isoindole-1,3-dione (PP-33) and its 4,5,6,7-tetrafluoro deriv. (FPP-33) augmented 12-O-tetradecanoylphorbol 13-acetate-induced prodn. by human leukemia HL-60 cells of both tumor necrosis factor alpha (TNF-.alpha.) mRNA and secreted TNF-.alpha. protein. Intracellular TNF-.alpha. protein prodn. was increased to a lesser extent.
IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(augmentation by phthalimides of phorbol ester-induced expression of tumor necrosis factor-.alpha. message)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

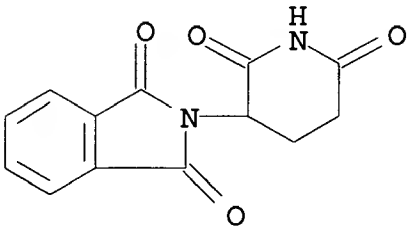


L84 ANSWER 6 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:439973 HCAPLUS
DOCUMENT NUMBER: 125:157748
TITLE: Inducer-specific bidirectional regulation by thalidomide and phenylphthalimides of tumor necrosis factor-.alpha. production
AUTHOR(S): Miyachi, Hiroyuki; Azuma, Akihiko; Hioki, Erika; Iwasaki, Shigeo; Kobayashi, Yoshiro; Hashimoto, Yuichi
CORPORATE SOURCE: Inst. Mol. Cell. Biosci., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Biochem. Biophys. Res. Commun. (1996), 224(2), 426-430
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Regulation by thalidomide [N(.alpha.)-phthalimidoglutarimide] of tumor necrosis factor (TNF)-.alpha. prodn. was found to be inducer-specific. Thalidomide enhances TNF-.alpha. prodn. by human leukemia HL-60 cells induced with 12-O-tetradecanoylphorbol 13-acetate (TPA), while it inhibits TNF-.alpha. prodn. induced with okadaic acid (OA) in the same cell line. Some phthalimide analogs, including PP-33 [2-(2,6-diisopropylphenyl)-1H-isoindole-1,3-dione] and its 4,5,6,7-tetrafluoro deriv. (FPP-33), also showed such an inducer-specific bidirectional TNF-.alpha. prodn.-regulating activity. The structure-activity relationships of the compds. tested are similar, but not identical, in the TPA-stimulated HL-60 and OA-stimulated HL-60 assay systems.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(inducer-specific bidirectional regulation by thalidomide and phenylphthalimides of tumor necrosis factor-.alpha.

prodn. by human leukemia cells)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



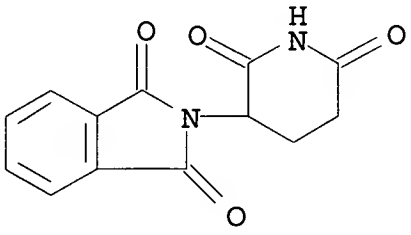
L84 ANSWER 7 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:423443 HCAPLUS
DOCUMENT NUMBER: 125:104687
TITLE: Thalidomide inhibits tumor necrosis factor .alpha., decreases nitric oxide synthesis, and ameliorates the hyperdynamic circulatory syndrome in portal-hypertensive rats
AUTHOR(S): Lopez-Talavera, Juan Carlos; Cadelina, Gregory; Olchowski, Jeannette; Merrill, William; Groszmann, Roberto J.
CORPORATE SOURCE: School Medicine, Yale University, West Haven, CT, 06516, USA
SOURCE: Hepatology (Philadelphia) (1996), 23(6), 1616-1621
CODEN: HPTLD9; ISSN: 0270-9139
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A hyperdynamic circulatory state frequently is obsd. in portal hypertension with liver failure or extensive portal-systemic shunting. Tumor necrosis factor .alpha. (TNF) causes marked hypotension in mammals by inducing nitric oxide synthesis and has been shown to play a role in the development of the hemodynamic changes obsd. in portal hypertension. Thalidomide selectively inhibits TNF prodn. by enhancing mRNA degrdn. We investigated the systemic and portal hemodynamic effects of thalidomide in a prehepatic model of portal hypertension and evaluated whether suppressing TNF synthesis decreases NO prodn. Portal hypertension was induced by partial ligation of the portal vein (PVL). Animals

received thalidomide (T) (50 mg/kg/d) + water or water alone (W), orally, daily for 2 days before and 13 days after PVL operation, at which time hemodynamic studies were performed and TNF plasma levels were obtained. Sham-operated animals were studied identically. In an addnl. group of PVL animals, 24-h urinary excretion of NO-2 and NO-3 was measured during treatment. PVL animals receiving T presented with a significantly higher mean arterial pressure and systemic vascular resistance and significantly lower portal pressure, TNF plasma levels, and 24-h urinary excretion of NO-2 and NO-3, in comparison with rats receiving W. A significant correlation ($r = -0.61$) was obsd. between TNF plasma levels and mean arterial pressure among PVL animals. Thalidomide did not have any significant effects on sham rats. Thalidomide inhibits TNF synthesis and reduces NO prodn., blunts the development of the hyperdynamic circulation, and decreases portal pressure in PVL-operated rats.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide inhibits tumor necrosis factor .alpha., decreases nitric oxide synthesis, and ameliorates the hyperdynamic circulatory syndrome in portal-hypertensive rats)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 8 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1996:422680 HCAPLUS

DOCUMENT NUMBER: 125:104270

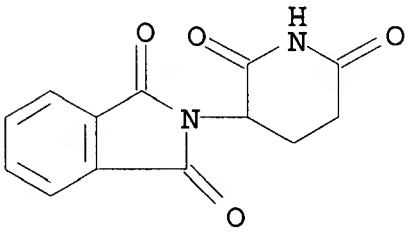
TITLE: Potent Inhibition of Tumor Necrosis Factor-.alpha. Production by Tetrafluorothalidomide and Tetrafluorophthalimides

AUTHOR(S): Niwayama, Satomi; Turk, Benjamin; Liu, Jun
CORPORATE SOURCE: Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: J. Med. Chem. (1996), 39(16), 3044-3045
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CJACS-IMAGE; CJACS

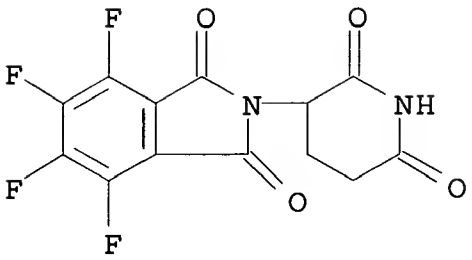
AB The authors synthesized a series of tetrafluorophthalimide derivs. which are potent inhibitors of LPS-induced TNF-.alpha. prodn. Although they exhibit higher cytotoxicity to cells than thalidomide, inhibition of LPS-induced TNF-.alpha. prodn. by these analogs occurs well under their cytotoxic concns. and is therefore specific. As these tetrafluorophthalimide derivs. are much more potent than thalidomide, they may serve as new tools to dissect the lipopolysaccharide-mediated signaling pathway leading to TNF-.alpha. prodn. Given the roles of TNF-.alpha. in inflammation and septic shock, these compds. may serve as leads for novel therapeutic agents.

IT 50-35-1, Thalidomide 179033-21-7
179033-22-8 179033-23-9
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potent inhibition of TNF-.alpha. prodn. by tetrafluorothalidomide and tetrafluorophthalimides)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 179033-21-7 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-4,5,6,7-tetrafluoro- (9CI) (CA INDEX NAME)



RN 179033-22-8 HCAPLUS
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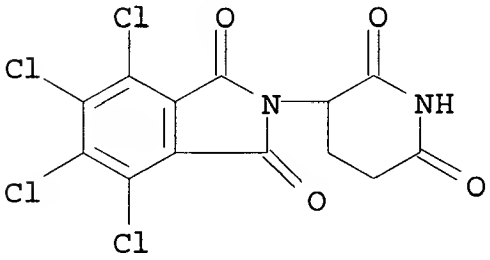
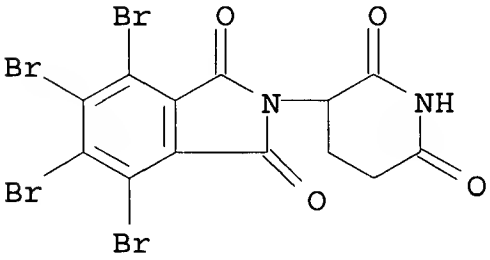


RN 179033-23-9 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4,5,6,7-tetrabromo-2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



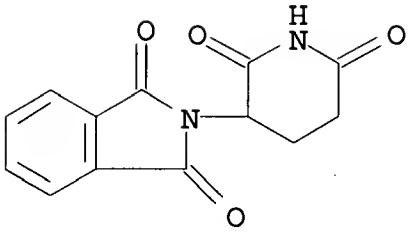
L84 ANSWER 9 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:420312 HCAPLUS
DOCUMENT NUMBER: 125:103957

TITLE: Thalidomide in autoimmune conditions
AUTHOR(S): Gardner-Medwin, Janet M.
CORPORATE SOURCE: Clinical Immunology, Univ. Hospital, Nottingham, NG7 2UH, UK
SOURCE: Expert Opin. Invest. Drugs (1996), 5(7), 829-841
CODEN: EOIDER; ISSN: 0967-8298
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 141 refs. Thalidomide remains a household name 35 yr after the disaster caused by its teratogenic properties. Its use re-emerged when the therapeutic benefit of thalidomide in lepromatous leprosy was recognized, and it continues to be used in a small no. of patients with a variety of conditions for whom there is no therapeutic alternative. Thalidomide's unique and numerous pharmacol. properties have maintained research interest, most recently concg. on the inhibition of both tumor necrosis factor and angiogenesis. These may be important pharmacol. mechanisms in those clin. conditions where it has proven therapeutic benefit. Thalidomide is beneficial in idiopathic oral and genital ulceration, and the similar ulceration of Behcet's disease and human immunodeficiency virus (HIV) infection. In addn., it is of value in chronic graft-vs.-host disease, lepromatous leprosy and in a no. of rare dermatoses. However, the current use of thalidomide is overshadowed by the tragedy of around 12,000 children affected by its teratogenic potential between 1959-1961. The use of thalidomide must, therefore, be limited to patients who have failed on alternative therapies, and must always promote the safest possible use of this valuable therapeutic agent.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide in autoimmune conditions)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

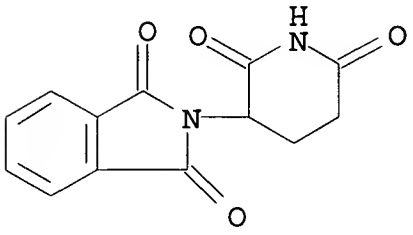


L84 ANSWER 10 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:411415 HCAPLUS
DOCUMENT NUMBER: 125:75647
TITLE: The effect of thalidomide on experimental tumors and metastases
AUTHOR(S): Minchinton, Andrew I.; Fryer, Karen H.; Wendt, Karen R.; Clow, Kathy A.; Hayes, Malcolm M. M.
CORPORATE SOURCE: Dep. Med. Biophys., BC Cancer Res. Cent., Vancouver, BC, V5Z 1L3, Can.
SOURCE: Anti-Cancer Drugs (1996), 7(3), 339-343
CODEN: ANTDEV; ISSN: 0959-4973
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of thalidomide on growth, radiosensitivity and metastasis was studied in murine SCCVII and Lewis Lung tumors. Daily thalidomide administration (0.77 mmol/kg/day, i.p.) did not alter primary tumor growth of SCCVII or Lewis Lung tumors. However, thalidomide did reduce the radiosensitivity of the Lewis Lung tumor and increased its sensitivity to combined treatment with radiation and the bioreductive cytotoxin tirapazamine. These findings suggest that thalidomide elevates tumor hypoxia in the Lewis Lung tumor, presumably via an antiangiogenic mechanism. Also, thalidomide reduced the incidence of lung metastases from primary Lewis Lung tumors. Thalidomide may therefore have utility in the management of solid tumors, esp. when combined with drugs that are selectively toxic to cells at reduced O tension (e.g., bioreductive cytotoxins).

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor and antimetastatic action of)
RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 11 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:301952 HCAPLUS
DOCUMENT NUMBER: 125:8209
TITLE: Multinucleated giant cell formation of swine microglia induced by Mycobacterium bovis
AUTHOR(S): Peterson, Phillip K.; Gekker, Genya; Hu, Shuxian; Anderson, W. Robert; Teichert, Matthew; Chao, Chun C.; Molitor, Thomas W.
CORPORATE SOURCE: Medical School, University Minnesota, Minneapolis, USA
SOURCE: J. Infect. Dis. (1996), 173(5), 1194-1201
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English

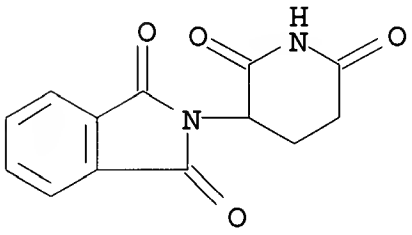
AB Multinucleated giant cells (MGC) have been long recognized as a histopathol. feature of tuberculosis, yet little is known about the underlying mechanism of tubercle bacillus-induced formation of these fused macrophages. The main purpose of this study was to characterize cellular mechanisms involved in MGC formation of swine microglia, the resident macrophages of the brain, in cultures contg. nonopsonized Mycobacterium bovis. Within 2 h of incubation, MGC were readily detected in these cultures by light and transmission electron microscopy. MGC formation was blocked by anti-CD14 and anti-CD18 antibodies and by thalidomide, a potent inhibitor of tumor necrosis factor-.alpha. (TNF-.alpha.) prodn. by microglia. Also, TNF-.alpha. alone induced MGC formation. These findings suggest that two microglial cell receptors, CD14 and a .beta.2 integrin, and the cytokine TNF-.alpha. participate in M. bovis-induced swine microglial MGC formation.

IT 50-35-1, Thalidomide

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(multinucleated giant cell formation of swine microglia induced by Mycobacterium bovis inhibition by)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 12 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1996:286067 HCAPLUS

DOCUMENT NUMBER: 125:771

TITLE: Synergistic effects of thalidomide and poly(ADP-ribose) polymerase inhibition on type II collagen-induced arthritis in mice

AUTHOR(S): Kroeger, Hans; Miesel, Ralf; Dietrich, Annette; Ohde, Manuela; Rajnavoelgyi, Eva; Ockenfels, Heinrich

CORPORATE SOURCE: Department Biochemistry, German Rheumatology Research Center, Berlin, Germany

SOURCE: Inflammation (N. Y.) (1996), 20(2), 203-215
CODEN: INFLD4; ISSN: 0360-3997

DOCUMENT TYPE: Journal

LANGUAGE: English

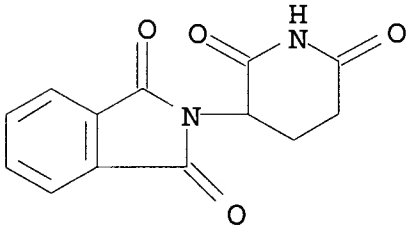
AB The present study investigates synergistic effects of the TNF-.alpha. inhibitor thalidomide and the poly(ADP-ribose) polymerase (PARP)-inhibitor nicotinic acid amide (NAA) in male DBA/1 hybrid mice suffering from type II collagen-induced arthritis. Parameters including the arthritis index, chemiluminescence and anti-collagen antibody titers were used for the assessment of disease activity. The disease courses demonstrated clearly an inhibitory effect of thalidomide. NAA inhibited established collagen arthritis in a dose-dependent manner. The combined application of thalidomide and NAA caused a powerful synergistic

inhibition of arthritis. Furthermore, thalidomide and NAA were tested ex vivo for their inhibition of the NADPH oxidase-dependent generation of reactive oxygen species by activated neutrophils and monocytes in unsepd. human blood. Our data show that type II collagen-induced arthritis can be suppressed by the simultaneous inhibition of TNF-.alpha., PARP, and NADPH oxidase.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic effects of thalidomide and nicotinic acid amide on type II collagen-induced arthritis in mice)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 13 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1996:225320 HCAPLUS

DOCUMENT NUMBER: 124:306605

TITLE: The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection

AUTHOR(S): Klausner, Jeffrey D.; Makonkawkeyoon, Sanit; Akarasewi, Pasakorn; Nakata, Koh; Kasinrerk, Watchara; Corral, Laura; Dewar, Robin L.; Lane, H. Clifford; Freedman, Victoria H.; Kaplan, Gilla

CORPORATE SOURCE: Medical Center, New York University, New York, USA

SOURCE: J. Acquired Immune Defic. Syndr. Hum. Retrovirol. (1996), 11(3), 247-57
CODEN: JDSRET; ISSN: 1077-9450

DOCUMENT TYPE: Journal

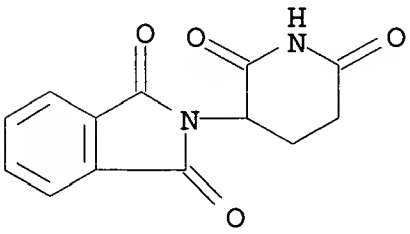
LANGUAGE: English

AB Tumor necrosis factor alpha (TNF-.alpha.), a cytokine produced during the host defense against infection, is assocd. with fevers, weakness, and progressive wt. loss. Thalidomide inhibits the synthesis of TNF-.alpha. both in vitro and in vivo and may have clin. usefulness. The authors therefore initiated a pilot study of thalidomide treatment in patients with human immunodeficiency virus type 1 (HIV-1)-assocd. wasting with or without concomitant infection with tuberculosis. Thirty-nine patients were randomly allocated to treatment with either thalidomide or placebo in a double-blind manner for 21 days. Thirty-two patients completed the study. In patients with concomitant HIV-1 and tuberculosis infections, thalidomide therapy was assocd. with a redn. in both plasma TNF-.alpha. levels and HIV-1 levels. No significant redn. in either TNF-.alpha. or HIV-1 levels was obsd. in patients with HIV-1 infection only. During the study period, patients receiving thalidomide treatment showed a significant wt. gain (: 6.5%) relative to placebo-treated patients. Patients with simultaneous HIV-1 and tuberculosis infections experienced a higher mean wt. gain during thalidomide treatment than the group of patients with HIV-1 infection only. The results of this pilot study suggest that thalidomide may have a clin. role in enhancing wt. gain and possibly reducing TNF-.alpha. and HIV-1 levels in patients with HIV-1 and concomitant mycobacterial infections.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of thalidomide on pathogenesis of human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in relation to tumor necrosis factor alpha prodn.)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

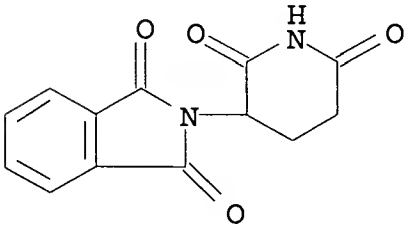


L84 ANSWER 14 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:208788 HCAPLUS
DOCUMENT NUMBER: 124:306835
TITLE: Thalidomide can be either agonistic or antagonistic to LPS evoked synthesis of TNF-.alpha. by mononuclear cells
AUTHOR(S): Shannon, Edward J.; Sandoval, Felipe
CORPORATE SOURCE: Gillis W. Long Hansen's Disease Center, Louisiana State University, Baton Rouge, LA, USA
SOURCE: Immunopharmacol. Immunotoxicol. (1996), 18(1), 59-72
CODEN: IITOEF; ISSN: 0892-3973
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of thalidomide on tumor necrosis factor alpha (TNF-.alpha.) produced in vitro by lipopolysaccharide (LPS) stimulated human cells was investigated. In cultures of LPS stimulated human mononuclear cells enriched for adherent cells and in cultures of LPS stimulated human monocytes of the cell line-THP-1, thalidomide enhanced the synthesis of TNF-.alpha.. When cultures of un-fractionated peripheral blood mononuclear cells were stimulated with LPS, thalidomide decreased the synthesis of TNF-.alpha.. Depending on the type of cells stimulated with LPS in vitro, thalidomide, at concns. achieved in vivo, can either enhance or suppress the synthesis of TNF-.alpha..

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect of thalidomide on LPS evoked synthesis of TNF-.alpha. by mononuclear cells)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

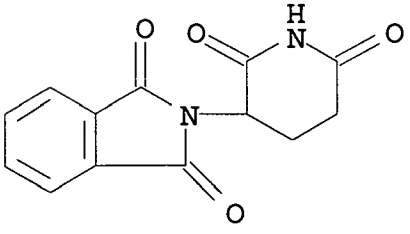


L84 ANSWER 15 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:186715 HCAPLUS
DOCUMENT NUMBER: 124:278433
TITLE: Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade
AUTHOR(S): Geitz, Hartmut; Handt, Stefan; Zwingenberger, Kai
CORPORATE SOURCE: Department of Pathology, Rheinisch-Westfaelische Technische Hochschule (RWTH), Aachen, Germany
SOURCE: Immunopharmacology (1996), 31(2-3), 213-21
CODEN: IMMUDP; ISSN: 0162-3109
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mode of action of thalidomide (THD) in clin. cases of vasculitis is still not clear. Expression of adhesion mols. on endothelial cell lines was therefore assessed in vitro. THD is capable of changing the d. of tumor necrosis factor .alpha. (TNF.alpha.) induced ICAM-1 (CD54), VCAM-1 (CD106) and E-selectin antigens on HUVEC. Furthermore, modulation of L-selectin (CD62L) by THD can be demonstrated on human leukocytes in vitro. The mols. investigated are involved in the neutrophil-endothelial cell interaction and participate in the adhesion cascade. Blunting of cytokine induced up-regulation of these adhesion mols. may account at least in part for anti-vasculitic effects of thalidomide.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide selective modulation of d. of cell surface mols. involved in adhesion cascade)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

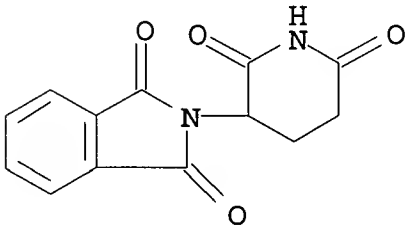


L84 ANSWER 16 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:163597 HCAPLUS
DOCUMENT NUMBER: 124:278812
TITLE: Thalidomide for aphthous ulcers in patients infected with the human immunodeficiency virus
AUTHOR(S): Weidle, Paul J.
CORPORATE SOURCE: Department Pharmacy Services, University Maryland, Baltimore, MD, 21201, USA
SOURCE: Am. J. Health-Syst. Pharm. (1996), 53(4), 368, 371-2, 378
CODEN: AHSPEK; ISSN: 1079-2082
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The AIDS Clin. Trials Group has confirmed the efficacy of thalidomide 200 mg/day for oral ulcers in HIV-infected patients. Thalidomide also appears to benefit most HIV-infected patients with aphthous ulcers of the esophagus or rectum. The optimal dosage of thalidomide for the treatment of aphthous ulcers is unknown. A dosage of 200 mg once daily at bedtime is reasonable. A response should be noted within a few days to weeks.

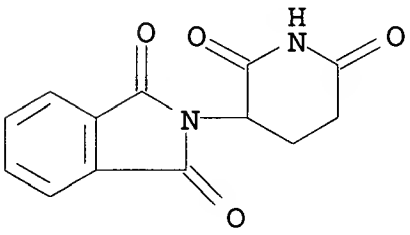
IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide for aphthous ulcers in patients infected with the human immunodeficiency virus)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 17 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:110612 HCAPLUS
DOCUMENT NUMBER: 124:193680
TITLE: Effect of thalidomide on the inflammatory response in cerebrospinal fluid in experimental bacterial meningitis
AUTHOR(S): Burroughs, Margaret H.; Tsenova-Berkova, Liana; Sokol, Karen; Ossig, Joachim; Tuomanen, Elaine; Kaplan, Gilla
CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, NY, USA
SOURCE: Microb. Pathog. (1995), Volume Date 1995, 19(4), 245-55
CODEN: MIPAEV; ISSN: 0882-4010
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In exptl. bacterial meningitis in rabbits, the inflammatory process is largely mediated by cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-.alpha. (TNF-.alpha.). Since thalidomide has been shown to inhibit TNF-.alpha. prodn., expts. were carried out to det. whether the drug can modulate the inflammatory response to either lysates of Hemophilus influenzae (gram neg.) or heat-killed Streptococcus pneumoniae (gram pos.) in rabbits. The introduction of a lysate of H. influenzae into the cerebrospinal fluid (CSF) of rabbits caused a very acute inflammatory response, as indicated by a rapid increase in TNF-.alpha. levels in the CSF and a concomitantly rapid leukocytosis. In contrast, the introduction of heat-killed S. pneumoniae induced a more indolent inflammatory response, which also waned more slowly. Thalidomide treatment reduced TNF-.alpha. prodn. in both exptl. systems but had a greater effect on the more indolent gram-pos. inflammatory response, in which peak TNF-.alpha. levels in the CSF were reduced by >50%. Also, a sustained inhibition of leukocytosis was obsd. in the inflammatory response to heat-killed gram-pos. bacteria. In meningeal inflammation induced by the gram-neg. lysate, treatment with thalidomide resulted in only a 29% inhibition of TNF-.alpha. release into the CSF. In contrast to the drug effect on TNF-.alpha., thalidomide treatment did not significantly affect IL-1 levels in these models of rabbit bacterial meningitis.
IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL

(Biological study)
(inflammatory response in cerebrospinal fluid in exptl. bacterial meningitis response to)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



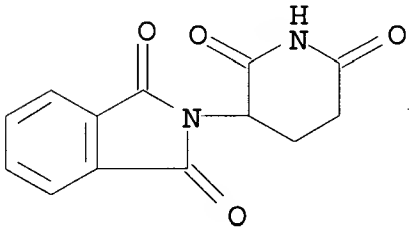
L84 ANSWER 18 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1996:104155 HCAPLUS
DOCUMENT NUMBER: 124:193633
TITLE: Thalidomide promotes metastasis of prostate adenocarcinoma cells (PA-III) in L-W rats
AUTHOR(S): Pollard, Morris
CORPORATE SOURCE: Lobund Laboratory, University of Notre Dame, Notre Dame, IN, 46556, USA
SOURCE: Cancer Lett. (Shannon, Irel.) (1996), 101(1), 21-4
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two contradictory actions have been ascribed to thalidomide relative to tumor metastasis: immunosuppression and antiangiogenesis. The latter effect was detd. with basic fibroblast growth factor in a rabbit cornea micropocket assay system. The prostate adenocarcinoma (PA-III) transplanted tumor line in Lobund-Wistar (L-W) rats produces a tumor at the s.c. implant site from which tumor cells metastasize uniformly only through lymphatic channels through the heart to the lungs in which secondary tumors develop. L-W rats were implanted with PA-III cells and administered, by gavage, thalidomide (50 mg/kg body wt. per day) in corn oil. Control rats with PA-III cells were administered corn oil. Autopsy examns. on day 30 revealed that the

thalidomide-treated rats developed more metastatic tumor foci in the lungs than in the controls. Thus, thalidomide does not appear to have an inhibitory effect in tumor metastasis.

IT 50-35-1, Thalidomide
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide promotes metastasis of prostate adenocarcinoma cells (PA-III) in L-W rats)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 19 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1996:6455 HCAPLUS

DOCUMENT NUMBER: 124:75710

TITLE: The effect of thalidomide on BCG-induced granulomas in mice

AUTHOR(S): Aarestrup, F.M.; Goncalves-da-Costa, S.C.; Sarno, E.N.

CORPORATE SOURCE: Faculdade de Odontologia, Universidade Federal de Juiz de Fora, Juiz de Fora, 36100-000, Brazil

SOURCE: Braz. J. Med. Biol. Res. (1995), Volume Date 1995, 28(10), 1069-76
CODEN: BJMRDK; ISSN: 0100-879X

DOCUMENT TYPE: Journal

LANGUAGE: English

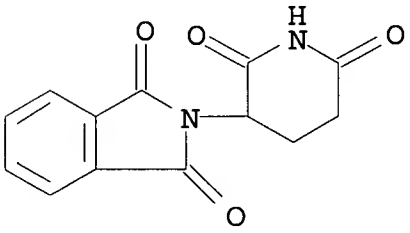
AB Granuloma proliferation is the result of a series of complex biol. events in which a variety of cell types and cytokines are involved. Tumor necrosis factor alpha (TNF-.alpha.) plays a central role. In the present study, we investigated the effect of thalidomide (.alpha.-N-pthalimidoglutarimide), a selective inhibitor of TNF-.alpha. synthesis, on granuloma formation during BCG

infection in Oncins France 1 (OF-1) mice. S.c. injections of 30 mg/kg body wt. of thalidomide daily for 14, 21 or 28 days into the mice resulted in the redn. of the size and total no. of liver granulomas. The most striking effect of thalidomide was obsd. after 28 days, when the total no. of liver granulomas was reduced by as much as 40% ($P<0.05$). Serum TNF-.alpha. levels of thalidomide-treated mice were significantly lower (85%) than control mice on day 14 and remained lower (55%) on days 21 and 28. Pos. immunohistochem. staining specific for TNF-.alpha. was demonstrable only in well-developed granulomas in which central mononuclear cells presented extensive differentiation into epithelioid cells. Daily administration of thalidomide for 21 to 28 days to the BCG-infected mice inhibited local TNF-.alpha. expression in well-developed granulomas. The mechanisms by which thalidomide modulates the granuloma proliferation are discussed.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(thalidomide effect on BCG-induced granulomas)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 20 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER:	1995:964769 HCAPLUS
DOCUMENT NUMBER:	124:44421
TITLE:	Inhibitors of TNF .alpha. synthesis
AUTHOR(S):	Davidsen, Steven K; Summers, James B
CORPORATE SOURCE:	Department 47J, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE:	Expert Opin. Ther. Pat. (1995), Volume Date 1995, 5(10), 1087-100 CODEN: EOTPEG; ISSN: 1354-3776

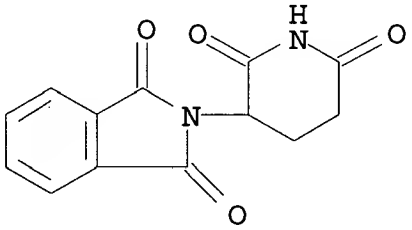
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 135 refs. Tumor necrosis factor-.alpha. (TNF .alpha.) is a cytokine with a multitude of biol. activities linked to the pathol. of inflammation. Current anti-TNF .alpha. strategies include several protein-based approaches, one of which has produced pos. results in the clinic. Most of the small mols. which specifically inhibit TNF .alpha. prodn. do so by increasing intracellular cyclic adenosine monophosphate (cAMP) which ultimately blocks TNF .alpha. gene expression. The most important of these compds. are the rolipram and pentoxifylline-related phosphodiesterase IV (PDE IV) inhibitors which are being actively pursued by a no. of pharmaceutical companies. The ability of thalidomide to block TNF .alpha. prodn. contributes to its therapeutic properties in humans. Recent studies suggest that cell-assocd. TNF .alpha. may be necessary for normal host defense mechanisms. This finding has added to the excitement concerning the identification of a unique metalloproteinase enzyme which is responsible for the proteolytic processing of TNF .alpha.. Inhibitors of this matrix metalloproteinase-related enzyme have appeared in both the primary and patent literature. The therapeutic benefit of small mol. inhibitors of TNF .alpha. synthesis will likely be assessed in the near future.

IT 50-35-1, Thalidomide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of TNF .alpha. synthesis by)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 21 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:932481 HCAPLUS
DOCUMENT NUMBER: 124:21626

TITLE: Thalidomide inhibits tumor necrosis factor-.alpha. production by lipopolysaccharide- and lipoarabinomannan-stimulated human microglial cells

AUTHOR(S): Peterson, Phillip K.; Hu, Shuxian; Sheng, Wen S.; Kravitz, Frederic H.; Molitor, Thomas W.; Chatterjee, Delphi; Chao, Chun C.

CORPORATE SOURCE: Medical School, University Minnesota, Minneapolis, MN, 55415, USA

SOURCE: J. Infect. Dis. (1995), 172(4), 1137-40
CODEN: JIDIAQ; ISSN: 0022-1899

DOCUMENT TYPE: Journal

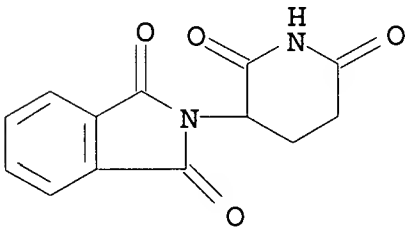
LANGUAGE: English

AB Tumor necrosis factor-.alpha. (TNF-.alpha.) is a pathogenic factor in bacterial meningitis. The effect of thalidomide on TNF-.alpha. prodn. by microglia, the resident macrophages of the brain, was evaluated. In primary human fetal microglial cell cultures stimulated with lipopolysaccharide or lipoarabinomannan, thalidomide inhibited TNF-.alpha. release in a dose-dependent manner. The inhibitory effect of thalidomide was similar to that of dexamethasone, although expression of TNF-.alpha. mRNA in microglial cells was reduced only by thalidomide. The results of this in vitro study suggest that thalidomide could have therapeutic potential in gram-neg. bacterial and tuberculous meningitis.

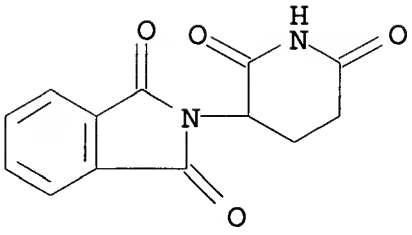
IT 50-35-1, Thalidomide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide inhibition of TNF-.alpha. prodn. in human microglial cells in relation to gram-neg. bacterial and tuberculous meningitis treatment)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 22 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:905985 HCAPLUS
DOCUMENT NUMBER: 124:75518
TITLE: Benzylphthalimides and phenethylphthalimides with thalidomide-like activity on the production of tumor necrosis factor .alpha.
AUTHOR(S): Sasaki, Keizo; Shibata, Yoshihiro; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. Molecular Cellular Biosci., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Biol. Pharm. Bull. (1995), 18(9), 1228-33
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Benzylphthalimide analogs (PIP's) and phenethylphthalimide analogs (P2P's) show thalidomide-like activity on the prodn. of tumor necrosis factor (TNF)-.alpha. by the human leukemia cell line, HL-60, stimulated by 12-O-tetradecanoylphorbol-13-acetae (TPA). Structure-activity relations are discussed on the basis of the TNF-.alpha. prodn.-enhancing activity. Benzylphthalimide (PIP-00) exhibited activity which is weaker than that of thalidomide, but introduction of a Me group at the ortho-position of the benzyl moiety (PIP-10) resulted an increase to a level comparable with that of thalidomide. Phenethylphthalimide (P2P-00) is more potent than thalidomide, and its fluorinated deriv., 2-phenethyl-4,5,6,7-tetrafluoro-1H-isoindole-1,3-dione, exhibited potent activity at very low concns.
IT 50-35-1, Thalidomide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thalidomide-like activity of benzyl- and phenethylphthalimides on prodn. of tumor necrosis factor-.alpha.)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 23 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:835168 HCAPLUS
DOCUMENT NUMBER: 123:329934
TITLE: DNA oxidation as a potential molecular mechanism mediating drug-induced birth defects: phenytoin and structurally related teratogens initiate the formation of 8-hydroxy-2'-deoxyguanosine in vitro and in vivo in murine maternal hepatic and embryonic tissues
AUTHOR(S): Liu, Ling; Wells, Peter G.
CORPORATE SOURCE: Fac. of Pharmacy, Univ. of Toronto, Toronto, ON, Can.
SOURCE: Free Radical Biol. Med. (1995), 19(5), 639-48
CODEN: FRBMEH; ISSN: 0891-5849
DOCUMENT TYPE: Journal
LANGUAGE: English

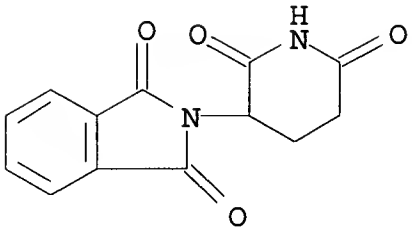
AB A considerable no. of teratogens, including the anticonvulsant drug phenytoin and structurally related drugs and environment chems., may be bioactivated by peroxidases, such as prostaglandin H synthase (PHS) and lipoxygenases (LPOs), to a reactive free radical intermediate that initiates birth defects. However, the mol. targets of the reactive free radical intermediates mediating chem. teratogenesis, and hence the fundamental determinants of susceptibility, are poorly understood. In these studies, a teratogenic dose of phenytoin (65 mg/kg), when injected into pregnant CD-1 mice during organogenesis on gestational day 12, initiated the oxidn. of DNA in maternal hepatic and embryonic nuclei, forming 8-hydroxy-2'-deoxyguanosine. Significant maternal and embryonic DNA oxidn. occurred at 6 and 3 h, resp., suggesting relative embryonic deficiencies in free radical-related cytoprotective enzymes, although the rates appeared similar. Maximal DNA oxidn. in both maternal and embryonic tissues occurred at 6 h, presumably reflecting the balance of DNA oxidn. and repair,

the latter of which appeared similar in both tissues. Inhibition of phenytoin-initiated embryonic DNA oxidn. by the free radical spin trapping agent .alpha.-phenyl-N-t-butylnitrone (41.5 mg/kg), and by acetylsalicylic acid (10 mg/kg), an inhibitor of the cyclooxygenase component of PHS, was consistent with the previously reported redn. by these inhibitors of phenytoin-initiated murine birth defects. In vitro studies using a horseradish peroxidase (0.5 mg/mL)-H2O2 (5.45 .mu.g/mL) bioactivating system for drug-initiated oxidn. of 2'-deoxyguanosine (3.74 mM), indicated that the potency of xenobiotic-initiated formation of 8-hydroxy-2'-deoxyguanosine for the structurally related drugs and metabolites phenytoin, 5-(p-hydroxyphenyl)-5-phenylhydantoin, trimethadione, dimethadione, l-mephenytoin, l-nirvanol, d-nirvanol (80 .mu.M each), or thalidomide (64 .mu.M), reflected their murine teratogenic potency. Given the relatively low activities of cytochromes P 450, compared to PHS and LPOs, in human and rodent embryonic tissues, these data support the potential teratol. importance of peroxidase-catalyzed embryonic DNA oxidn. may constitute a crit. mol. mechanism mediating the teratogenicity of phenytoin and related drugs and environmental chems., and suggest the potential teratol. importance of peroxidase-catalyzed bioactivation of xenobiotics with structural similarities to phenytoin. These studies provide the first evidence that peroxidase-catalyzed embryonic DNA oxidn. may constitute a crit. mol. mechanism mediating the teratogenicity of phenytoin and related drugs and environmental chems., and suggest the potential teratol. importance of addnl. embryonic processes, such as DNA repair and tumor suppressor genes, as determinants of susceptibility.

IT 50-35-1, Thalidomide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(DNA oxidn. as mol. mechanism of teratogenesis since phenytoin and structurally related teratogens initiate formation of hydroxydeoxyguanosine in vitro and in vivo in murine maternal hepatic and embryonic tissues)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 24 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:790081 HCAPLUS
DOCUMENT NUMBER: 123:217935
TITLE: Does thalidomide affect IL-2 response and production?
AUTHOR(S): Fernandez, Luis P.; Schlegel, Paul G.; Baker, Jeanette; Chen, Yanfei; Chao, Nelson J.
CORPORATE SOURCE: Medical Center, Stanford University, Stanford, CA, 94305, USA
SOURCE: Exp. Hematol. (Charlottesville, Va.) (1995), Volume Date 1995, 23(9), 978-85
CODEN: EXHMA6; ISSN: 0301-472X
DOCUMENT TYPE: Journal
LANGUAGE: English

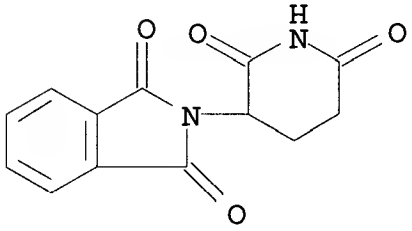
AB The exact mechanism of immunosuppression by thalidomide is poorly understood. A common denominator in the pathogenesis of graft-vs.-host disease, graft rejection, reactional lepromatous leprosy, and autoimmune disorders modulated by thalidomide is the activation of T lymphocytes culminating in the synthesis of interleukin-2 (IL-2), the expression of high-affinity IL-2 receptors, and the induction of proliferation. The authors investigated the effect of thalidomide on the prodn. of IL-2 by the human leukemia cell line Jurkat through induction of IL-2 gene enhancer activity and through the presence of IL-2 in supernatants. .beta.-Galactosidase activity, encoded by a reporter lac z construct and controlled by a transcription factor in thalidomide-treated PMA- and ionomycin-stimulated Jurkat cells, was similar (97%) to non-thalidomide-treated controls at all drug concns. tested. IL-2 enhancer-driven .beta.-galactose activity of thalidomide-treated and stimulated cells was also similar to that of untreated controls. The IL-2 prodn. of activated nontransfected Jurkat cells was gauged by using the IL-2-dependent cell line HT-2 as a readout and by ELISA. Jurkat cells were subcloned by limiting

diln. Bulk cultures and three subclones (J.5.2.5., J.5.2.9., and J.5.3.8.) were assayed at 6, 12, and 24 h after PHA/PMA-induced stimulation. No inhibitory effect on the IL-2 prodn. by thalidomide could be detected at any of the drug concns. tested (5-30 .mu.g/mL), whereas 10 to 100 ng/mL of cyclosporine inhibited the IL-2 prodn. by 95 to 100%. In addn., the authors obsd. neither inhibition of IL-2-dependent proliferation of HT-2 nor inhibition of PHA-induced proliferation of peripheral mononuclear cells by thalidomide at all drug concns. used (5-30 .mu.g/mL). These results do not support the possibility of a modulatory effect on the immune response by thalidomide via IL-2 prodn. and IL-2 response.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(does thalidomide affect IL-2 response and prodn.)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 25 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1995:750173 HCAPLUS

DOCUMENT NUMBER: 123:160120

TITLE: Effect of thalidomide on tumor necrosis factor production and antitumor activity induced by 5,6-dimethylxanthenone-4-acetic acid

AUTHOR(S): Ching, L.-M.; Xu, Z.-F.; Gummer, B. H.; Palmer, B. D.; Joseph, W. R.; Baguley, B. C.

CORPORATE SOURCE: Cancer Res. Lab., Univ. of Auckland School of Medicine, Auckland, 1000, N. Z.

SOURCE: Br. J. Cancer (1995), 72(2), 339-43
CODEN: BJCAAI; ISSN: 0007-0920

DOCUMENT TYPE: Journal

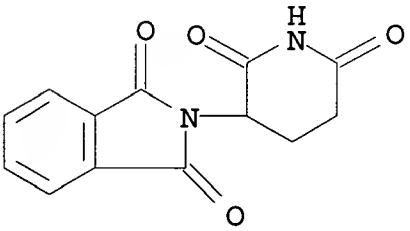
LANGUAGE: English

AB The effect of pharmacol. suppression of tumor necrosis factor (TNF) prodn. on the antitumor activity of 5,6-dimethylxanthenone-4-acetic acid (5,6-MeXAA) was examd. in mice, taking advantage of previous observations that TNF prodn. in response to endotoxin in vitro is inhibited by thalidomide. Thalidomide at 8-250 mg/kg efficiently suppressed serum TNF activity in mice in response to 5,6-MeXAA at its optimal TNF-inducing dose of 55 mg/kg. Suppression was achieved when thalidomide was administered at the same time as, or .ltoreq.4 h before, 5,6-MeXAA. Under conditions in which TNF activity was suppressed, the degree of tumor hemorrhagic necrosis and the proportion of cures of the s.c. colon 38 tumor were increased. In mice administered thalidomide (100 mg/kg) together with 5.6-MeXAA (30 mg/kg), complete tumor regression was obtained in 100% of the animals, as compared with 67% in mice receiving 5,6-MeXAA alone. The results suggest a possible new application for thalidomide and pose new questions about the action of 5,6-MeXAA and related compds.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor necrosis factor prodn. and antitumor activity of dimethylxanthenoneacetic acid response to)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 26 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1995:645378 HCAPLUS

DOCUMENT NUMBER: 123:74416

TITLE: Thalidomide treatment reduces tumor necrosis factor .alpha. production and enhances weight gain in patients with pulmonary

tuberculosis

AUTHOR(S): Tramontana, Jane M.; Utaipat, Utaiwan; Molloy, Anthony; Akarasewi, Pasakorn; Burroughs, Margaret; Makonkawkeyoon, Sanit; Johnson, Barbara; Klausner, Jeffrey D.; Rom, William; Kaplan, Gilla

CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, NY, 10021, USA

SOURCE: Mol. Med. (Cambridge, Mass.) (1995), 1(4), 384-97
CODEN: MOMEF3; ISSN: 1076-1551

DOCUMENT TYPE: Journal

LANGUAGE: English

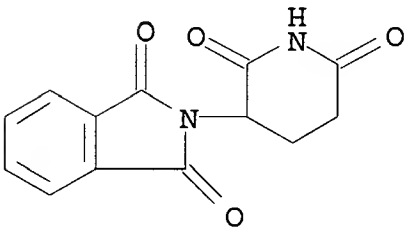
AB The monocyte-derived cytokine, tumor necrosis factor .alpha. (TNF.alpha.), is essential for host immunity, but overprodn. of this cytokine may have serious pathol. consequences. Excess TNF.alpha. produced in pulmonary tuberculosis may cause fevers, weakness, night sweats, necrosis, and progressive wt. loss. Thalidomide (.alpha.-N-phthalimidoglutarimide) has recently been shown to suppress TNF.alpha. prodn. by human monocytes in vitro and to reduce serum TNF.alpha. in leprosy patients. We have therefore conducted a two-part placebo-controlled pilot study of thalidomide in patients with active tuberculosis to det. its effects on clin. response, immune reactivity, TNF.alpha. levels, and wt. 30 Male patients with active tuberculosis, either human immunodeficiency virus type 1 pos. (HIV-1+) or HIV-1-, received thalidomide or placebo for single or multiple 14 day cycles. Toxicity of the study drug, delayed type hypersensitivity (DTH), cytokine prodn., and wt. gain were evaluated. Thalidomide treatment was well tolerated, without serious adverse events. The drug did not adversely affect the DTH response to purified protein deriv. (PPD), total leukocyte, or differential cell counts. TNF.alpha. prodn. was significantly reduced during thalidomide treatment while interferon-.gamma. (IFN.gamma.) prodn. was enhanced. Daily administration of thalidomide resulted in a significant enhancement of wt. gain. The results indicate that thalidomide is well tolerated by patients receiving anti-tuberculosis therapy. Thalidomide treatment reduces TNF.alpha. prodn. both in vivo and in vitro and is assocd. with an accelerated wt. gain during the study period.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thalidomide reduces tumor necrosis factor .alpha. prodn. in patients with pulmonary tuberculosis)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 27 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1995:583145 HCAPLUS

DOCUMENT NUMBER: 122:312425

TITLE: TNF.alpha. regulation of HIV1: Biology and therapy

AUTHOR(S): Kaplan, G.; Moreira, A. L.

CORPORATE SOURCE: Rockefeller University, New York, NY, 10021, USA

SOURCE: Res. Immunol. (1994), 145(8-9), 685-9
CODEN: RIMME5; ISSN: 0923-2494

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

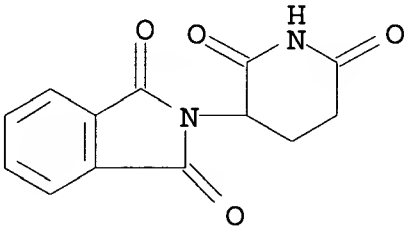
AB A review and discussion with 17 refs. Tumor necrosis factor .alpha. appears to have central role in the regulation of HIV-1 replication in vivo. Any perturbation in TNF.alpha. formation would thus be expected to be assocd. with changes in HIV-1 replication and disease progression. In an attempt to inhibit TNF.alpha. prodn. in patients, the authors also evaluated the effects of thalidomide treatment on cytokine levels and on cytokine-induced immunopathol.

IT 50-35-1, Thalidomide

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide effect on tumor necrosis factor .alpha. regulation of HIV-1)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 28 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:533428 HCAPLUS
DOCUMENT NUMBER: 122:282172
TITLE: The effect of thalidomide and supidimide on endotoxin-induced uveitis in rats
AUTHOR(S): Guex-Crosier, Yan; Pittet, Nancy; Herbort, Carl Peter
CORPORATE SOURCE: Hopital Jules Gonin, University Lausanne, Lausanne, CH-1004, Switz.
SOURCE: Graefe's Arch. Clin. Exp. Ophthalmol. (1995), 233(2), 90-3
CODEN: GACODL; ISSN: 0721-832X
DOCUMENT TYPE: Journal
LANGUAGE: English

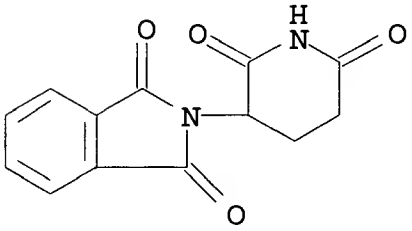
AB Endotoxin-induced uveitis (EIU) is an animal model of ocular inflammation, produced by footpad injection of endotoxin (lipopolysaccharide, LPS) to mimic the human disease of acute anterior uveitis, that is useful for testing new anti-inflammatory therapy. The purpose of this study was to test the anti-inflammatory effect on EIU of thalidomide and one of its derivs., supidimide. EIU was produced in rats by hind footpad injection of LPS (100 .mu.g/animal). Animals were killed 20 h after LPS injection. Inflammation was evaluated by anterior chamber detn. of proteins and cells. A dosage of 400 mg/kg per day of thalidomide was efficient in reducing inflammation whether given in three doses (at -24 h, -4 h and +4 h relative to LPS challenge = THAL-1; p<0.001 for proteins and cells), in two doses (-4 h and +4 h = THAL-2; p<0.001 for proteins, p.ltoreq.0.012 for cells) or in one dose (at +4 h = late THAL; p<0.001 for proteins, p.ltoreq.0.02 for cells). A dosage of 300 mg/kg per day of thalidomide was still efficient (p.ltoreq.0.023 for proteins, p.ltoreq.0.06 for cells), but 150 mg/kg per day had no effect on inflammation. Supidimide (400 mg/kg

per day) had some anti-inflammatory effect (p.ltoreq.0.053 for proteins, p.ltoreq.0.06 for cells). High-dose thalidomide had a potent anti-inflammatory effect in EIU, but lower doses were not sufficient to reduce inflammation. At similar high doses, supidimide had some effect on EIU but was less effective than thalidomide.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide and supidimide effect on endotoxin-induced uveitis)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 29 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1995:440978 HCAPLUS

DOCUMENT NUMBER: 122:281418

TITLE: N-Alkylphthalimides: structural requirement of thalidomidal action on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor .alpha. production by human leukemia HL-60 cells

AUTHOR(S): Shibata, Yoshihiro; Shichita, Mizue; Sasaki, Keizo; Nishimura, Koji; Hashimoto, Yuichi; Iwasaki, Shigeo

CORPORATE SOURCE: Inst. Mol. and Cellular Biosci., Univ. Tokyo, Tokyo, 113, Japan

SOURCE: Chem. Pharm. Bull. (1995), 43(1), 177-9
CODEN: CPBTAL; ISSN: 0009-2363

DOCUMENT TYPE: Journal

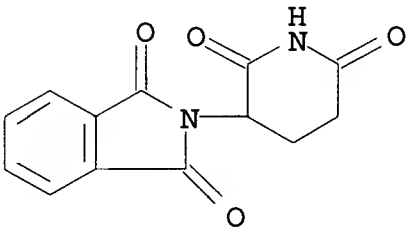
LANGUAGE: English

AB Phthalimide analogs N-substituted with Bu, tert-Bu, hexyl and

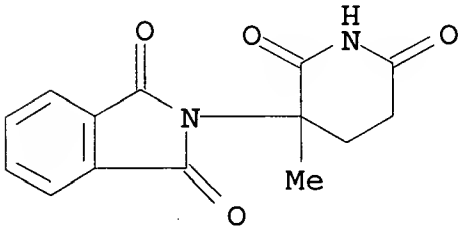
adamantyl groups were designed and prepd. as simplified analogs of thalidomide and methylthalidomide. All the compds. prepd. except N-n-butylphthalimide showed thalidomidal activity on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor (TNF)-.alpha. prodn. by human leukemia HL-60 cells. Among the investigated compds., including thalidomide and methylthalidomide, N-adamantylphthalimide showed the most potent TNF-.alpha. prodn.-enhancing activity.

IT 50-35-1, Thalidomide 162662-87-5
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of alkylphthalimides and structural requirement on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor .alpha. prodn. by human leukemia HL-60 cells)

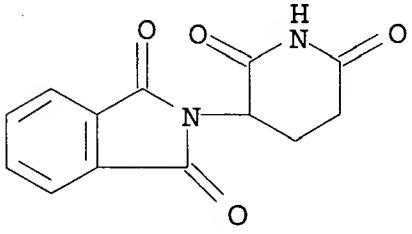
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 162662-87-5 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

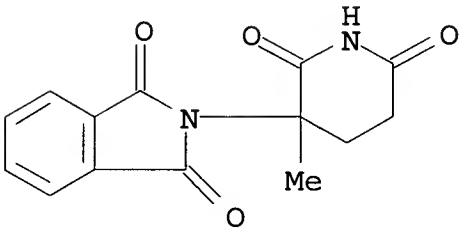


L84 ANSWER 30 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:440220 HCAPLUS
DOCUMENT NUMBER: 122:255537
TITLE: Enhancement of 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor .alpha. production by phenethylphthalimide analogs
AUTHOR(S): Sasaki, Keizo; Shibata, Yoshihiro; Nishimura, Koji; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. Mol. Cellular Bio., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Biol. Pharm. Bull. (1994), 17(9), 1313-15
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of phenyl-, benzyl-, phenethyl-, and phenylpropylphthalimides on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced tumor necrosis factor (TNF)-.alpha. prodn. by the human leukemia cell line HL-60 were examd. Among the four phthalimide derivs., only phenethylphthalimide showed potent enhancing effect on TNF-.alpha. prodn.
IT 50-35-1 162662-87-5
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor .alpha. prodn. by phenethylphthalimide analogs)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 162662-87-5 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)-

(9CI) (CA INDEX NAME)



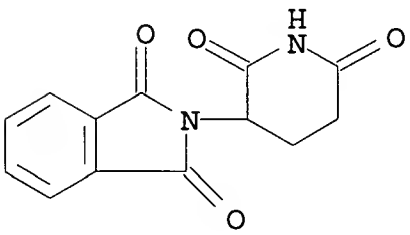
L84 ANSWER 31 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:439216 HCAPLUS
DOCUMENT NUMBER: 122:204749
TITLE: The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures
AUTHOR(S): Mchugh, S. M.; Rifkin, I. R.; Deighton, J.; Wilson, A. B.; Lachmann, P. J.; Lockwood, C. M.; Ewan, P. W.
CORPORATE SOURCE: Molecular Immunopathology Unit, MRC Centre, Cambridge, CB2 2QH, UK
SOURCE: Clin. Exp. Immunol. (1995), 99(2), 160-7
CODEN: CEXIAL; ISSN: 0009-9104
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thalidomide is an effective immunomodulatory drug in man, but its mechanism of action remains unclear. The authors hypothesized that, in addn. to its reported inhibitory effects on prodn. of monocyte-derived tumor necrosis factor-alpha (TNF-.alpha.), thalidomide might be effective at the level of Th immunoregulation. In a comparative study with the immunosuppressant cyclosporin A, the authors have demonstrated a potent and specific effect of thalidomide on cytokine prodn. relating to the distinct Th1 and Th2 subsets. It induced and enhanced the prodn. of IL-4 and IL-5 and, at the same dose (1000 ng/mL), significantly inhibited interferon-gamma (IFN-.gamma.) prodn. in phytohemagglutinin (PHA)-stimulated human peripheral blood mononuclear cell (PBMC) cultures. Stimulation of PBMC with recall antigen (streptokinase: streptodornase (SKSD)) at 144h in the absence of thalidomide

resulted in a predominantly Th1 response, with the prodn. of IFN-.gamma. and IL-2. Thalidomide switched this response from a Th1 to a Th2 type. The effect was most pronounced at 1000 ng/mL thalidomide, where inhibition of IFN-.gamma. and enhancement of IL-4 prodn. was maximal. In unstimulated cultures, thalidomide alone induced IL-4 prodn. Cyclosporin A, in contrast, inhibited both Th1 and Th2 cytokine prodn. by PHA-stimulated PBMC. Time course data from thalidomide-treated cultures revealed that the augmented IL-4 prodn. diminished as the culture time increased, whereas IFN-.gamma. prodn. was significantly increased. This response might be due to activation-induced apoptosis of Th2 cells or the induction of Th2 cell anergy, in the continued presence of stimulating agents, with the emergence of IFN-.gamma.-secreting Th1 cells when Th2 antagonism declines. The effects of thalidomide and related compds. may enhance the authors understanding of the mechanisms of T helper cell selection, offer the possibility of controlled therapeutic switching between Th1 and Th2 responses, and may lead to a rational approach for the treatment of some T cell-mediated immunol. disorders.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine prodn. in mitogen- and antigen-stimulated human peripheral human blood mononuclear cell cultures)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



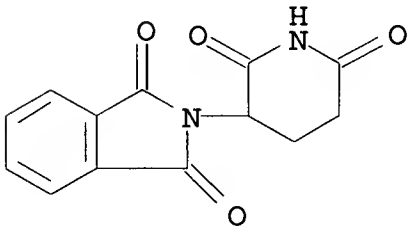
L84 ANSWER 32 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:437435 HCAPLUS
DOCUMENT NUMBER: 122:204574

TITLE: Enhancement of phorbol ester-induced production of tumor necrosis factor-.alpha. by 2,6-dimethylphenylphthalimide
AUTHOR(S): Shibata, Yoshihiro; Sasaki, Keizo; Nishimura, Koji; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Institute Molecular Cellular Biosciences, University Tokyo, Tokyo, 113, Japan
SOURCE: Biol. Pharm. Bull. (1994), 17(11), 1532-4
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of phenyl- and benzylphthalimide analogs on tumor necrosis factor (TNF)-.alpha. prodn. by a human leukemia cell line, HL-60, stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated. Though nonsubstituted phenyl- and benzylphthalimides had no effect on TNF-.alpha. prodn. after TPA stimulation, introduction of a Me group(s) onto the Ph group resulted in potent enhancement of TNF-.alpha. prodn. The most active compd. was 2,6-dimethylphenylphthalimide.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(phthalimide deriv. enhancement of tumor necrosis factor-.alpha. formation by human leukemia cells)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 33 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1995:430880 HCAPLUS
DOCUMENT NUMBER: 122:204735
TITLE: Thalidomide and supidimide downregulate the inflammation in endotoxin-induced

uveitis

AUTHOR(S): Guex-Crosier, Yan; Pittet, Nancy; Herbort, Carl P.

CORPORATE SOURCE: National Institutes Health, National Eye Institute, Bethesda, MD, 20892, USA

SOURCE: Int. Congr. Ser. (1994), 1068(Advances in Ocular Immunology), 237-40
CODEN: EXMDA4; ISSN: 0531-5131

DOCUMENT TYPE: Journal

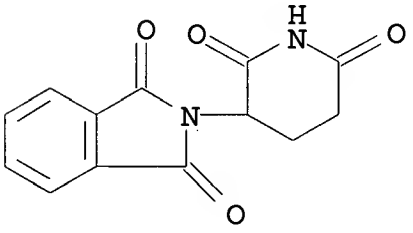
LANGUAGE: English

AB In rats with endotoxin-induced uveitis, the antiinflammatory effect of thalidomide was clearly seen with doses .gtoreq. 300 mg/kg/day, as shown by decreased protein exudation and anterior chamber cell infiltration. The thalidomide deriv. supidimide at 400 mg/kg/day in rats with endotoxin-induced uveitis decreased infiltration to a lesser degree than did thalidomide.

IT 50-35-1, Thalidomide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide and supidimide downregulate the inflammation in endotoxin-induced uveitis)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



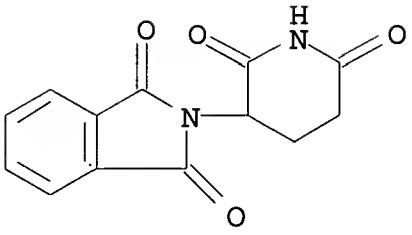
L84 ANSWER 34 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1995:403085 HCAPLUS

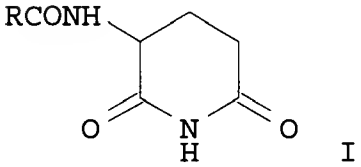
DOCUMENT NUMBER: 122:158437

TITLE: Pharmacologic inhibitors of tumor necrosis factor production exert differential effects in lethal endotoxemia and in infection with live microorganisms in mice

AUTHOR(S): Netea, Mihai G.; Blok, Willem L.; Kullberg, Bart-Jan; Bemelmans, Marc; Vogels, Maria T. E.; Buurman, Wim A.; Meer, Jos W. M. van der
CORPORATE SOURCE: Dept. Internal Medicine, University Hospital Nijmegen, Nijmegen, 6500 HB, Neth.
SOURCE: J. Infect. Dis. (1995), 171(2), 393-9
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-1.beta. (IL-1.beta.) are principal mediators of septic shock. Inhibition of TNF-.alpha. prodn. may ameliorate outcome in severe infections. Pentoxifylline, chlorpromazine, and thalidomide inhibit TNF-.alpha. prodn. Their effects were tested in lethal endotoxemia in sensitized mice. Only chlorpromazine significantly improved survival. Chlorpromazine and pentoxifylline significantly reduced postendotoxin circulating TNF-.alpha., by 89% and 76%, resp. Chlorpromazine also significantly reduced IL-1.beta. and sol. TNF receptor-P75. No drug improved survival in Klebsiella pneumoniae-infected mice despite significantly lower circulating TNF-.alpha. concns. in chlorpromazine- or pentoxifylline-treated animals. The three compds. decreased circulating TNF-.alpha. in Candida albicans-infected mice, but survival was not influenced. In neutropenic mice, chlorpromazine had no influence on candidae in organs, but in normal mice, Candida counts in kidneys were higher in chlorpromazine-treated mice. Thus, inhibition of TNF-.alpha. prodn. was of no benefit in K. pneumoniae infection and worsened outcome in C. albicans infection.
IT 50-35-1, Thalidomide
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibition of tumor necrosis factor prodn. by inhibitors do not reduce the septic shock death caused by Klesbsiella pneumoniae or Candida albicans)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 35 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1994:680507 HCAPLUS
DOCUMENT NUMBER: 121:280507
TITLE: Chemical modification of antineoplaston A10 and antitumor activity of its analogs
AUTHOR(S): Huang, Junqin; Ma, Weiyong; Zhang, Chunnian
CORPORATE SOURCE: Shanghai Inst. Pharm. Ind., Shanghai, 200040, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (1993), 24(10), 437-41, 451
CODEN: ZYGZEA; ISSN: 1001-8255
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



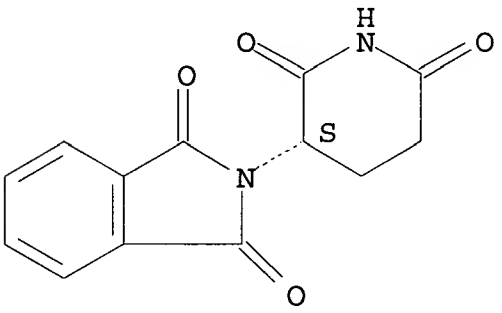
I

AB Antineoplaston A10 analogs I (R = benzyl, substituted benzyl, naphthylmethyl, thenyl, bromothenyl, PhCH:CH, etc.) were prepd. by N-acylation of 3-aminopiperidine-2,6-dione with RCO2H. I showed little or no activity at 100.mu.g/mL against L1210 leukemia cell.

IT 841-67-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

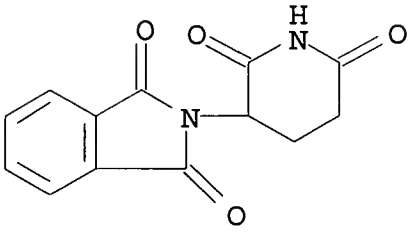
(prepn. and hydrazinolysis of)
RN 841-67-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L84 ANSWER 36 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1994:594752 HCAPLUS
DOCUMENT NUMBER: 121:194752
TITLE: Thalidomide. Expectation for lead material as biological response modifier (BRM)
AUTHOR(S): Hashimoto, Yuichi
CORPORATE SOURCE: Inst. Mol. Cell. Biosci., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Kagaku to Seibutsu (1994), 32(9), 604-8
CODEN: KASEAA; ISSN: 0453-073X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 11 refs. on the concept of BRM, development of thalidomide (I), use of I as an immunosuppressant, the relationship between optical activity of I and malformation-inducing activity, and I as a possible lead compd. in development of tumor necrosis factor-.alpha. formation enhancers or anticancer agents.
IT 50-35-1, Thalidomide
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(thalidomide as a possible lead compd. in the development of tumor necrosis factor-.alpha. formation enhancers as anticancer agents)
RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 37 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1994:473088 HCAPLUS
DOCUMENT NUMBER: 121:73088
TITLE: (S)-Form of .alpha.-methyl-N(.alpha.)-phthalimidoglutarimide, but not its (R)-form, enhanced phorbol ester-induced tumor necrosis factor-.alpha. production by human leukemia cell HL-60: implication of optical resolution of thalidomidal effects
AUTHOR(S): Nishimura, Koji; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. Mol. Cellular Biosciences, Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Chem. Pharm. Bull. (1994), 42(5), 1157-9
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

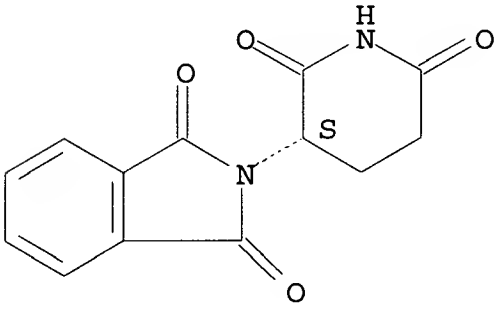
AB The rate of racemization of N(.alpha.)-phthalimidoglutarimide (thalidomide) was detd. as its half life to be 566 min at pH 7.4/37.degree.C. This fast racemization of thalidomide resulted in no apparent difference between (S)- and (R)-forms of the compd. on enhancing activity of phorbol ester-induced tumor necrosis factor (TNF)-.alpha. prodn. by human leukemia HL-60 cells. Optically pure forms of a structurally related analog of thalidomide, (S)- and (R)-.alpha.-methyl-N(.alpha.)-phthalimidoglutarimide (methylthalidomides), which do not racemize under the physiol. condition, were prepd. Only the (S)-form of methylthalidomide, but not its (R)-form, elicited TNF-.alpha. prodn.-enhancing effect, suggesting that the (S)-isomer of thalidomide would be the active form in terms of thalidomidal biol.

response modifying effects.

IT 841-67-8 2614-06-4
RL: BIOL (Biological study)
(tumor necrosis factor-.alpha. formation by human leukemia cell response to methylthalidomide stereoisomers in relation to)

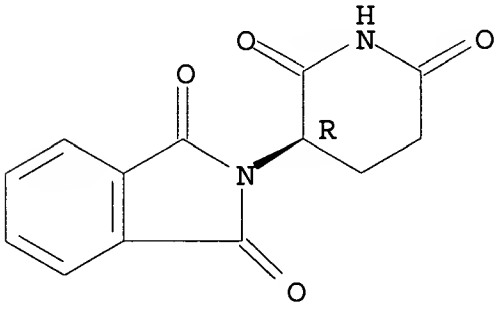
RN 841-67-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 2614-06-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (R)- (9CI) (CA INDEX NAME)

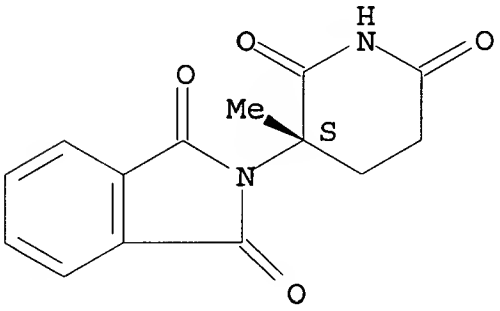
Absolute stereochemistry.



IT 108816-40-6 108816-41-7
RL: BIOL (Biological study)
(tumor necrosis factor-.alpha. formation by human leukemia cell response to, stereoisomerism in relation to)

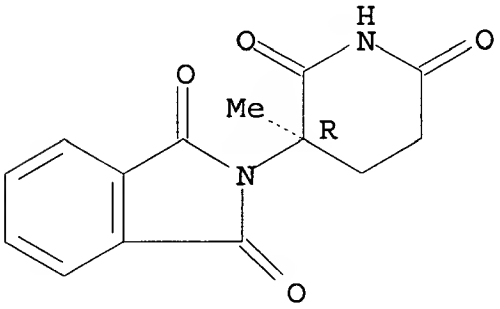
RN 108816-40-6 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 108816-41-7 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L84 ANSWER 38 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1994:314996 HCAPLUS
DOCUMENT NUMBER: 120:314996
TITLE: Thalidomide use in dermatology
AUTHOR(S): Ochonisky, Sophie; Revuz, Jean
CORPORATE SOURCE: Dep. Dermatol., Hop. Henri-Mondor, Creteil, 94010, Fr.
SOURCE: Eur. J. Dermatol. (1994), 4(1), 9-15
CODEN: EJDEE4; ISSN: 1167-1122
DOCUMENT TYPE: Journal; General Review

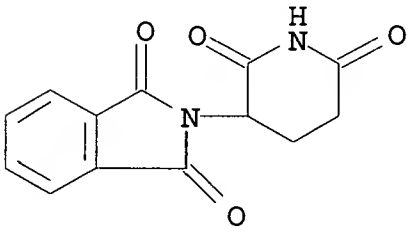
LANGUAGE: English

AB A review with 173 refs. Since the discovery of the dramatic efficacy of thalidomide in erythema nodosum leprosum, many works have demonstrated anti-inflammatory and immunosuppressive properties of this drug. During the past two decades, thalidomide has been shown to be effective in several dermatol. diseases such as actinic prurigo, discoid lupus erythematosus, prurigo nodularis, recurrent severe aphtosis, and Jessner's lymphocytic infiltration of the skin. Extra-dermatol. indications are now being tested, such as graft-vs.-host disease, rheumatoid arthritis or systemic lupus erythematosus. The precise way of thalidomide action remains unknown. The pharmacokinetics of the drug could explain in part its particular efficacy in muco-cutaneous disorders. Since the teratogenic effect of thalidomide can now be controlled, the neurotoxicity of the drug is now the principal factor limiting its use.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(dermatol. use of)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 39 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1994:260635 HCAPLUS

DOCUMENT NUMBER: 120:260635

TITLE: Enhancement of phorbol ester-induced production of tumor necrosis factor .alpha. by thalidomide

AUTHOR(S): Nishimura, Koji; Hashimoto, Yuichi; Iwasaki, Shigeo

CORPORATE SOURCE: Inst. Mol. Cell. Biosci., Univ. Tokyo, Tokyo, 113, Japan

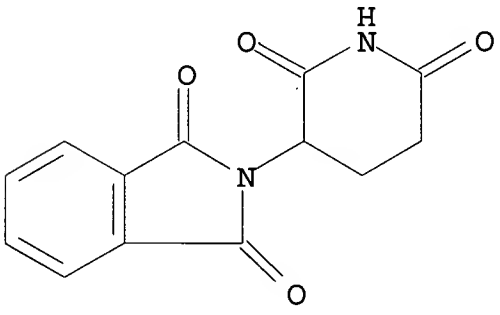
SOURCE: Biochem. Biophys. Res. Commun. (1994), 199(2), 455-60
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of thalidomide [racemic (DL-) form and optically pure (D- and L-) forms] on tumor necrosis factor (TNF) .alpha. prodn. by human leukemia cell lines (HL-60, K562 and U937) stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated. Though thalidomide has been regarded as a specific inhibitor of TNF-.alpha. prodn., the authors' study indicated that all forms of thalidomide enhanced (but did not inhibit) the TPA-induced TNF-.alpha. prodn. by the human leukemia cell lines investigated. The effects of thalidomide on TNF-.alpha. prodn. might be cell type-specific.

IT 731-40-8 841-67-8 2614-06-4
RL: BIOL (Biological study)
(tumor necrosis factor-.alpha. formation stimulation by, in human leukemia cells)

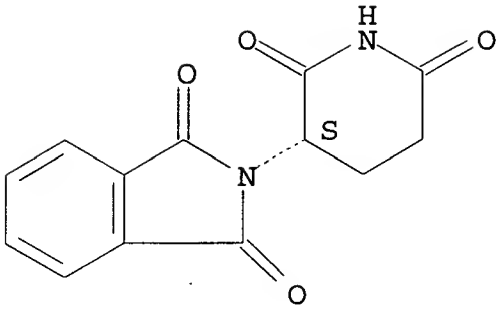
RN 731-40-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (.+-.)- (9CI) (CA INDEX NAME)

Racemate.



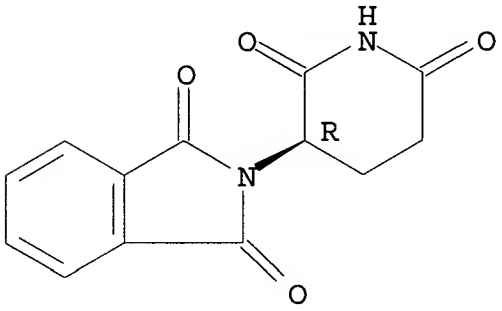
RN 841-67-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 2614-06-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



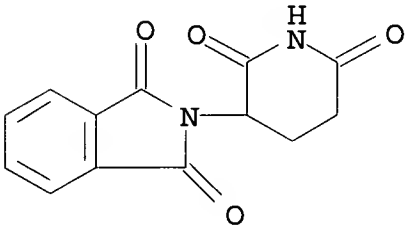
L84 ANSWER 40 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1994:214219 HCAPLUS
DOCUMENT NUMBER: 120:214219
TITLE: Inhibition of tumor necrosis factor-alpha by thalidomide in magnesium deficiency
AUTHOR(S): Weglicki, William B.; Stafford, Richard E.; Dickens, Benjamin F.; Mak, I. Tong; Cassidy, Marie M.; Phillips, Terry M.
CORPORATE SOURCE: Med. Cent., George Washington Univ., Washington, DC, 20037, USA
SOURCE: Mol. Cell. Biochem. (1993), 129(2), 195-200
CODEN: MCBIB8; ISSN: 0300-8177
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of thalidomide on circulating cytokines and myocardial lesion formation was investigated in Mg-deficient rats. After two weeks on a Mg-deficient diet, rats show an increase in circulating levels of tumor necrosis factor-alpha and interleukin 1. Thalidomide (1 mg/day) caused a complete inhibition of the increase in circulating tumor necrosis factor-alpha levels, without having an effect in interleukin 1. However, a marked increased in cardiomyopathic lesion formation was obsd. in Mg-deficient animals treated with thalidomide; possible mechanisms for thalidomide's enhancement of myocardial injury are discussed.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(interleukin-1 and tumor necrosis factor-.alpha. response to, in magnesium-deficient cardiomyopathy)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 41 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1993:508464 HCAPLUS

DOCUMENT NUMBER: 119:108464

TITLE: Thalidomide inhibits the replication of human immunodeficiency virus type 1

AUTHOR(S): Makonkawkeyoon, Sanit; Limson-Pobre, Rhona N. R.; Moreira, Andre L.; Schauf, Victoria; Kaplan, Gilla

CORPORATE SOURCE: Rockefeller Univ., New York, NY, 10021, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(13), 5974-8
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

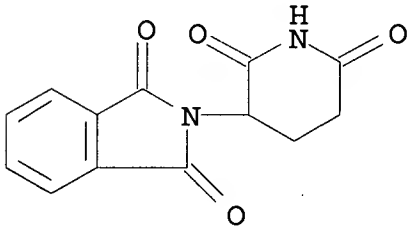
AB Thalidomide, a selective inhibitor of tumor necrosis

factor .alpha. (TNF-.alpha.) synthesis, suppresses the activation of latent human immunodeficiency virus type 1 (HIV-1) in a monocytoid (U1) line. The inhibition is dose dependent and occurs after exposure of the cells to recombinant TNF-.alpha., phorbol myristate acetate, lipopolysaccharide, and other cytokine combinations. Assocd. with HIV-1 inhibition is a redn. in agonist-induced TNF-.alpha. protein and mRNA prodn. Thalidomide inhibition of virus replication in the phorbol myristate acetate- and recombinant TNF-.alpha.-stimulated T-cell line ACH-2 is not obsd. The presence of thalidomide also inhibits the activation of virus in the peripheral blood mononuclear cells of 16 out of 17 patients with advanced HIV-1 infection and AIDS. These results suggest the use of thalidomide in a clin. setting to inhibit both virus replication and the TNF-.alpha.-induced systemic toxicity of HIV-1 and opportunistic infections.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(HIV-1 replication inhibition by, in T-lymphocytes and monocytes, in vitro and in humans)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 42 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1993:204908 HCAPLUS

DOCUMENT NUMBER: 118:204908

TITLE: Thalidomide exerts its inhibitory action on tumor necrosis factor .alpha. by enhancing mRNA degradation

AUTHOR(S): Moreira, Andre L.; Sampaio, Elizabeth P.; Zmuidzinas, Antonina; Frindt, Paula; Smith, Kendall A.; Kaplan, Gilla

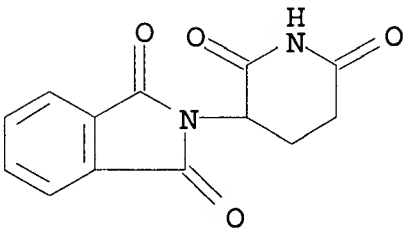
CORPORATE SOURCE: Dep. Cell. Physiol. Immunol., Rockefeller Univ.,

New York, NY, 10021, USA
SOURCE: J. Exp. Med. (1993), 177(6), 1675-80
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of thalidomide inhibition of lipopolysaccharide (LPS)-induced tumor necrosis factor .alpha. (TNF-.alpha.) prodn. was examd.; the drug enhanced the degrdn. of TNF-.alpha. mRNA. The half-life of the mol. was reduced from .apprx.30 to .apprx.17 min in the presence of 50 .mu.g/mL of thalidomide. Inhibition of TNF-.alpha. prodn. was selective, as other LPS-induced monocyte cytokines were unaffected. Pentoxifylline and dexamethasone, two other inhibitors of TNF-.alpha. prodn., are known to exert their effects by means of different mechanisms, suggesting that the three agents inhibit TNF-.alpha. synthesis at distinct points of the cytokine biosynthetic pathway. These observations provide an explanation for the synergistic effects of these drugs. The selective inhibition of TNF-.alpha. prodn. makes thalidomide an ideal candidate for the treatment of inflammatory conditions where TNF-.alpha.-induced toxicities are obsd. and where immunity must remain intact.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(tumor necrosis factor-.alpha. mRNA degrdn. enhancement by, anti-inflammatory activity in relation to)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 43 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1993:11605 HCAPLUS
DOCUMENT NUMBER: 118:11605
TITLE: Improvements in solubility and stability of

thalidomide upon complexation with hydroxypropyl-.beta.-cyclodextrin

AUTHOR(S): Krenn, Martina; Gamcsik, Michael P.; Vogelsang, Georgia B.; Colvin, O. Michael; Leong, Kam W.

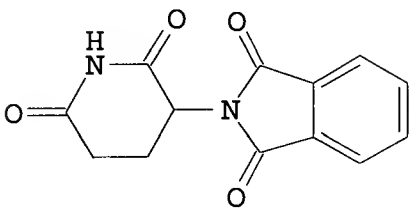
CORPORATE SOURCE: Dep. Biomed. Eng., Johns Hopkins Univ., Baltimore, MD, 21218, USA

SOURCE: J. Pharm. Sci. (1992), 81(7), 685-9
CODEN: JPMSAE; ISSN: 0022-3549

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



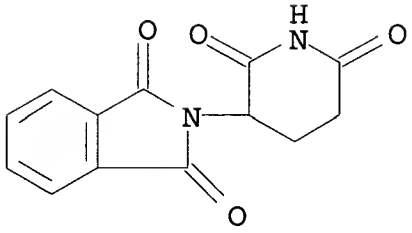
I

AB Thalidomide (I) is in clin. use for the treatment of graft-vs.-host disease in leukemia patients after bone marrow transplant. Low levels of the drug in plasma after oral administration have made an i.v. thalidomide formulation desirable. I, however, is sparingly sol. in aq. soln. (50 .mu.g/mL) and unstable. Complexation with hydroxypropyl .beta.-cyclodextrin (HP.beta.CD) has significantly improved the aq. soly. and stability of I. Results obtained with HPLC and NMR spectrometry have demonstrated that the soly. is increased to 1.7 mg/mL and the half-life of a dil. soln. is extended from 2.1 to 4.1 h. Hence, an i.v. I-HP.beta.CD in soln. has the potential to improve current therapy for graft-vs.-host disease by providing sustained high levels of drug in the plasma.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(solubilization and stabilization of, by hydroxypropyl .beta.-cyclodextrin complexation, for i.v. injections)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 44 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1992:212678 HCAPLUS
DOCUMENT NUMBER: 116:212678
TITLE: Prolonged treatment with recombinant interferon .gamma. induces erythema nodosum leprosum in lepromatous leprosy patients
AUTHOR(S): Sampaio, Elizabeth P.; Moreira, Andre L.; Sarno, Euzenir N.; Malta, Ana M.; Kaplan, Gilla
CORPORATE SOURCE: Lab. Cell. Physiol. Immunol., Rockefeller Univ., New York, NY, 10021, USA
SOURCE: J. Exp. Med. (1992), 175(6), 1729-37
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English

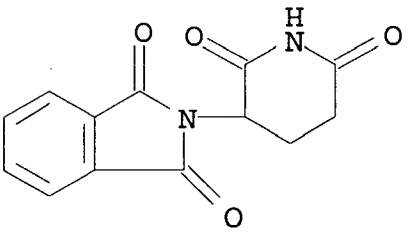
AB Patients with borderline and lepromatous leprosy were selected for a prolonged trial with recombinant interferon .gamma. (rIFN-.gamma.). Patients received 30 .mu.g intradermally for 6 injections over a 9-day period, and then either 100 .mu.g intradermally every 1 mo for 10 mo or every 2 wk for 5 mo (total, 1.2 mg). Erythema nodosum leprosum (ENL) was induced in 60% of the patients within 6-7 mo, as compared with an incidence of 15% per yr with multiple drug therapy alone. The mean whole-body redn. in bacterial index over the first 6 mo was 0.9 log units. Cutaneous induration at the intradermal injection sites of .gtoreq.15 mm predicted the development of a subsequent reactional state. Monocytes obtained from patients receiving the lymphokine demonstrated an increased respiratory burst and a 2.5-5.1-fold increase in tumor necrosis factor .alpha. (TNF-.alpha.) secretion in response to agonists. Patients in ENL had an even higher release of TNF-.alpha. from monocytes as well as high levels of TNF-.alpha. in the plasma (2000 pg/mL). Thalidomide therapy was required to treat the systemic manifestations of ENL. Control of toxic symptoms with thalidomide

was assocd. with a 50-80% redn. in agonist-stimulated monocyte TNF-.alpha. secretion. IFN-.gamma. enhanced the monocyte release of TNF-.alpha. by 3-7.5-fold (agonist dependent) when added to patient's cells in vitro, and this could be suppressed by the in vitro addn. of 10 .mu.g/mL of thalidomide.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(treatment with, tumor necrosis factor formation response to, in humans with lepromatous leprosy)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 45 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1991:441457 HCAPLUS

DOCUMENT NUMBER: 115:41457

TITLE: Induction of morphological differentiation in the human leukemic cell line K562 by exposure to thalidomide metabolites

AUTHOR(S): Hatfill, S. J.; Fester, E. D.; De Beer, D. P.; Bohm, L.

CORPORATE SOURCE: Fac. Med., Univ. Stellenbosch, Tygerberg, 7505, S. Afr.

SOURCE: Leuk. Res. (1991), 15(2-3), 129-36
CODEN: LEREDD; ISSN: 0145-2126

DOCUMENT TYPE: Journal

LANGUAGE: English

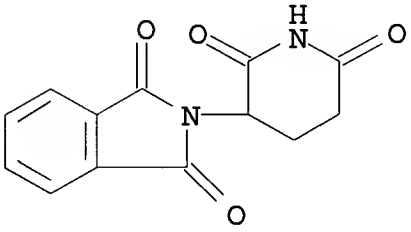
AB A single 2-h pulse exposure to thalidomide metabolites induced human leukemia K562 cells to undergo morphol. differentiation in vitro. The thalidomide metabolites (uncharacterized) were produced by a rabbit liver microsomal drug-metabolizing system. The differentiation was assessed by measuring several cell markers and

the expression of cell-surface antigens. A cytotoxic effect of the thalidomide metabolites was also demonstrated. The use of teratogenic drugs to alter gene expression may be a novel approach to the therapy of human leukemias.

IT 50-35-1D, Thalidomide, metabolites
RL: BIOL (Biological study)
(leukemia cells of humans differentiation by)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 46 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1991:156793 HCAPLUS

DOCUMENT NUMBER: 114:156793

TITLE: Thalidomide selectively inhibits tumor necrosis factor .alpha. production by stimulated human monocytes

AUTHOR(S): Sampaio, Elizabeth P.; Sarno, Euzenir N.; Galilly, Ruth; Cohn, Zanvil A.; Kaplan, Gilla

CORPORATE SOURCE: Lab. Cell. Physiol. Immunol., Rockefeller Univ., New York, NY, 10021, USA

SOURCE: J. Exp. Med. (1991), 173(3), 699-703
CODEN: JEMEAV; ISSN: 0022-1007

DOCUMENT TYPE: Journal

LANGUAGE: English

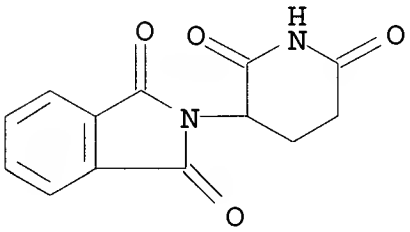
AB Thalidomide selectively inhibits the prodn. of human monocyte tumor necrosis factor-.alpha. (TNF-.alpha.) when these cells are triggered with lipopolysaccharide and other agonists in culture. A 40% inhibition occurs at the clin. achievable concn. of 1 .mu.g/mL. The amt. of total protein and individual proteins labeled with [35S]methionine detected by SDS-PAGE are not affected by thalidomide. The amts. of interleukin 1.beta. (IL-1.beta.), IL-6, and granulocyte/macrophage colony-stimulating factor produced by

monocytes remain unaltered. The selectivity of this drug may be useful in detg. the role of TNF-.alpha. in vivo and modulating its toxic effects in a clin. setting.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(monocyte prodn. of tumor necrosis factor .alpha. and interleukins and granulocyte-macrophage colony-stimulating factor response to, in human)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 47 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1989:52389 HCAPLUS

DOCUMENT NUMBER: 110:52389

TITLE: Evaluation of two in vitro assays to screen for potential developmental toxicants

AUTHOR(S): Steele, Vernon E.; Morrissey, Richard E.; Elmore, Eugene L.; Gurganus-Rocha, Deborah; Wilkinson, Betty P.; Curren, Rodger D.; Schmetter, Barry S.; Louie, Audrey T.; Lamb, James C., IV; Yang, Li L.

CORPORATE SOURCE: Northrop Services, Inc., Research Triangle Park, NC, 27709, USA

SOURCE: Fundam. Appl. Toxicol. (1988), 11(4), 673-84
CODEN: FAATDF; ISSN: 0272-0590

DOCUMENT TYPE: Journal

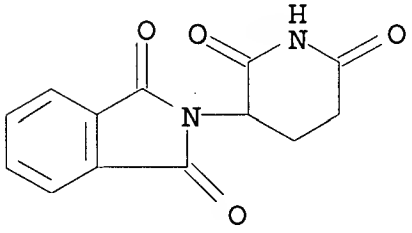
LANGUAGE: English

AB To evaluate two in vitro assays for their ability to detect known developmental toxicants and nontoxicants, a series of 44 coded compds. were assayed by 2 independent labs. using standardized protocols. The 2 test systems were the human embryonic palatal mesenchymal cell growth inhibition assay and the mouse ovarian

tumor cell attachment inhibition assay. After all compds. were tested, they were decoded and ranked according to the min. IC50 value (the millimolar concn. of compd. which inhibits growth or attachment by 50% compared to the solvent control) from either test. The in vitro test result concordance with established in vivo animal and human test results was examd. over a wide range of concn. levels (above which the in vitro results were called pos. and below which they were considered neg.). A pos. response from either test was defined as a pos. in vitro response. Concordance was defined as the no. of correct responses divided by the no. of chems. tested. At the 1-mM level, the concordance of data from the combined in vitro assays with the in vivo data was 66% in one lab. and 58% in the other. The max. agreement between the combined in vitro and in vivo data was reached at the 20-mM level, where there was a 73 and 74% concordance of results in the 2 labs. At that level, there was a 16 and 10% incidence of false neg. results, and a 54 and 77% incidence of false pos. results. A portion of these false neg. compds. may require metabolic activation. The use of either assay alone was not as accurate as using a pos. result from either test. Agreement of the in vitro data at the 10-mM level with available human data was 71 and 75% for each lab. Thus, 2 assays are complimentary and the combination of these assays could be useful as a preliminary screen to establish priorities for in vivo developmental toxicity testing.

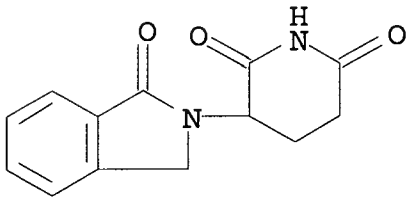
IT 50-35-1, Thalidomide 26581-81-7, EM-12
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of, to animal cell culture, teratogenicity in relation to)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 26581-81-7 HCAPLUS
CN 2,6-Piperidinedione, 3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI)

(CA INDEX NAME)



L84 ANSWER 48 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1987:613378 HCAPLUS
DOCUMENT NUMBER: 107:213378
TITLE: Prediction of teratogenic potential and a proposed scheme for teratogenicity screening of industrial research and development materials
AUTHOR(S): Lin, George H. Y.
CORPORATE SOURCE: Joseph C. Wilson Cent. Technol., Xerox Corp., Webster, NY, 14580, USA
SOURCE: In Vitro Toxicol. (1987), 1(3), 203-17
CODEN: IVTOE4; ISSN: 0888-319X
DOCUMENT TYPE: Journal
LANGUAGE: English

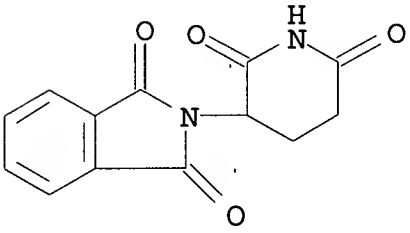
AB Data from the mouse ovary lectin-mediated attachment, the human embryo palatal mesenchyme cell growth inhibition, the mouse embryo limb bud cell culture, the whole embryo culture, the rat embryo midbrain and limb bud cell culture, the Drosophila embryo cell culture, and the differentiating neuroblastoma cell culture teratogenicity assays were classified into 3 endpoints: (1) inhibition of cell-to-cell interactions, (2) inhibition of cell growth, and (3) interference with cell differentiation. The sensitivity and specificity of each of the 7 assays are calcd. The Carcinogen Prediction and Battery Selection (CPBS) methodol. developed by Rosenkranz et al. (1985) is applied for the prediction of teratogens. Accordingly, the probabilities that the test chem. is a teratogen (P+) for compds. tested in the 7 assays are calcd. The calcd. results demonstrate that high correlation exists between the result of in vitro teratogenicity tests and in vivo data. In addn., P+ values for batteries contg. 3 assays, 1 from each endpoint, are calcd. Subsequently, a scheme for teratogenicity screening of industrial research and development materials is proposed. Research and development candidate materials may undergo

a selected battery of in vitro teratogenicity assays before the final decision for animal testing. Although in vitro teratogenicity assays cannot be used to substitute for animal tests, this procedure would achieve both cost-effectiveness and reducing animal tests in safety screening of materials.

IT 50-35-1, Thalidomide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(teratogenicity of, calcn. of potential for, in vitro assays in relation to)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 49 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1987:400437 HCAPLUS

DOCUMENT NUMBER: 107:437

TITLE: Investigation of the effect of thalidomide and dapsone on the respiratory burst of normal leukocytes

AUTHOR(S): Jenkins, J. S.; Powell, R. J.; Allen, B. R.

CORPORATE SOURCE: Queen's Med. Cent., Univ. Hosp., Nottingham, UK

SOURCE: Int. Congr. Symp. Ser. - R. Soc. Med. Serv. Ltd. (1986), 103(Recent Adv. Behcet's Dis.), 373-404
CODEN: RMISDU; ISSN: 0142-2367

DOCUMENT TYPE: Journal

LANGUAGE: English

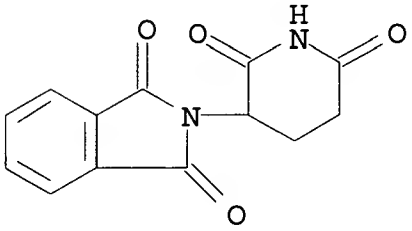
AB Histol. examn. of lesions in orogenital ulceration (OGU) reveals infiltration with neutrophils, lymphocytes, and monocytes. Thalidomide and dapsone have been used in severe idiopathic OGU; therefore, their effect was examd. on the respiratory burst of human neutrophils and monocytes. A chemiluminescent assay maximally stimulated with phorbol myristate acetate was used to measure the

overall respiratory burst with luminol enhancement. A similar assay was performed in using lucigenin as the enhancer to quantify superoxide prodn. The in vitro effects of thalidomide and dapsone on these assays was investigated by using therapeutically attainable dosages. The respiratory bursts of normal neutrophils and monocytes were unaffected by thalidomide. However, dapsone caused depression of both the respiratory burst and superoxide prodn. Apparently, dapsone and thalidomide exert their effects by different mechanisms.

IT 50-35-1, Thalidomide
RL: BIOL (Biological study)
(respiratory burst by human leukocyte response to)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 50 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1986:124742 HCAPLUS

DOCUMENT NUMBER: 104:124742

TITLE: Teratogen metabolism: thalidomide activation is mediated by cytochrome P 450

AUTHOR(S): Braun, Andrew G.; Harding, Fiona A.; Weinreb, Steven L.

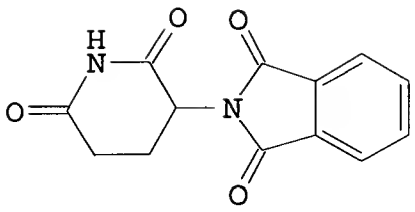
CORPORATE SOURCE: Dep. Appl. Biol. Sci., Massachusetts Inst. Technol., Cambridge, MA, 01239, USA

SOURCE: Toxicol. Appl. Pharmacol. (1986), 82(1), 175-9
CODEN: TXAPA9; ISSN: 0041-008X

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



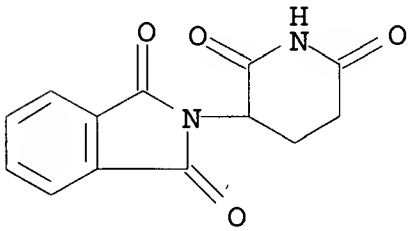
I

AB Metabolite of thalidomide (I) [50-35-1] generated by hepatic microsomes inhibited the attachment of tumor cells to concanavalin A-coated polyethylene. Evidence that metabolite formation is mediated by microsomal cytochrome P 450 [9035-51-2] is presented. Microsomes incubated with I underwent a type I spectral shift. Metabolite formation was reduced or eliminated by CO, SKF-525A [62-68-0], metyrapone [54-36-4], and N-octylamine [111-86-4]. Superoxide dismutase [9054-89-1] treatment had no effect. Metabolite formation required microsomes and NADPH and was dependent on the length of 37.degree. incubation. The metabolite could be isolated by successive hexane and CHCl3 extns. It is likely, the inhibitory I metabolite was generated by a minor cytochrome P 450 species. Whether this I metabolite is involved in the drug's teratogenic activity remains to be shown.

IT 50-35-1D, metabolites
RL: FORM (Formation, nonpreparative)
(formation of, in liver microsome, cytochrome P 450 in)

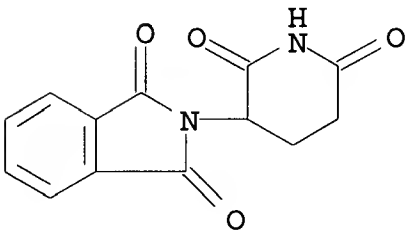
RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

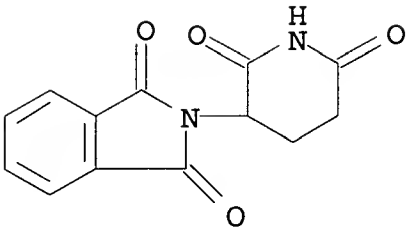


IT 50-35-1
RL: PROC (Process)
(metabolic activation of, by liver microsomes, cytochrome P 450 in)

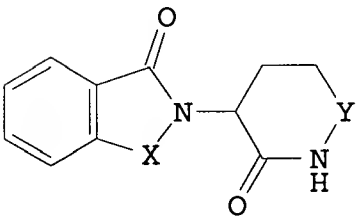
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 51 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1985:589756 HCAPLUS
DOCUMENT NUMBER: 103:189756
TITLE: Investigation and treatment of orogenital ulceration; studies on a possible mode of action of thalidomide
AUTHOR(S): Powell, R. J.; Allen, B. R.; Jenkins, J. S.; Steele, L.; Hunneyball, I.; Maurice, P. D. L.; Littlewood, S. M.
CORPORATE SOURCE: Univ. Hosp., Queen's Med. Cent., Nottingham, NG7 2UH, UK
SOURCE: Br. J. Dermatol., Suppl. (1985), 113(28), 141-4
CODEN: BJDSA9; ISSN: 0366-077X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In patients with orogenital ulceration, thalidomide [50-35-1] (40/ mg/day for 5 days followed by 200 mg/day for 23 days) induced full or partial resoln. of the ulcers. Thalidomide had no effects on leukocyte migration after 24 h in the carrageenan air pouch and carrageenan pleurisy models in the rat. Thus, it is unlikely that thalidomide acts on orogenital ulceration in Bahcet's syndrome by inhibiting leukocyte recruitment.
IT 50-35-1
RL: BIOL (Biological study)
(orogenital ulceration in Behcet's syndrome treatment with, leukocyte migration in relation to, in humans and lab. animals)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 52 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1985:555559 HCAPLUS
DOCUMENT NUMBER: 103:155559
TITLE: Teratogen metabolism: spontaneous decay products of thalidomide and thalidomide analogs are not bioactivated by liver microsomes
AUTHOR(S): Braun, Andrew G.; Weinreb, Steven L.
CORPORATE SOURCE: Dep. Appl. Biol. Sci., Massachusetts Inst. Technol., Cambridge, MA, 02139, USA
SOURCE: Teratog., Carcinog., Mutagen. (1985), 5(3), 149-58
CODEN: TCMUD8; ISSN: 0270-3211
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

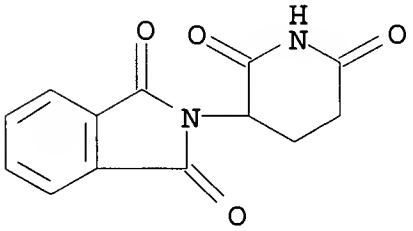


I, X=Y=CO
II, X=SO_2, Y=CH_2
III, X=CH_2, Y=CO

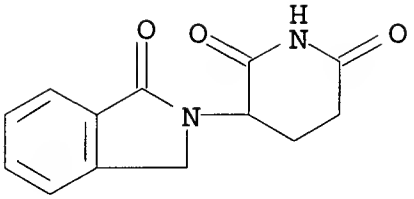
AB Thalidomide (I) [50-35-1] and 2 analogs, EM 87 (II) [49785-74-2], and EM 12 (III) [26581-81-7], inhibited the attachment of tumor cells to concanavalin A-coated surfaces if the drugs were 1st incubated with hepatic microsomes and

cofactors. Most agents that inhibit attachment are demonstrated teratogens. I underwent spontaneous hydrolysis to at least 12 products in saline buffered to a pH >7. These hydrolysis products did not inhibit attachment nor could they be activated to inhibitory products with hepatic microsomes. Similarly, II and III hydrolysis products were neither inhibitory nor substrates for activation. If the 3 drugs were incubated in buffered saline, there was a progressive decline in their ability to act as substrates for activation to an inhibitory product. It was possible to remove microsomes from the incubation mixt. following drug activation by centrifugation. This microsome-free mixt. inhibited cell attachment. When mouse ovarian tumor (MOT) cells were added to the microsome-free mixt., attachment was inhibited. However, if the activated drugs were incubated in saline, there was a progressive decline in their ability to inhibit attachment. Decay rates differed for the 3 compds. At a pH of 7.4, I, II, and III required 3, 1, and 6 h, resp., to decay to control levels. These relative rates of decay are consistent with the relative teratogenicity of the 3 drugs.

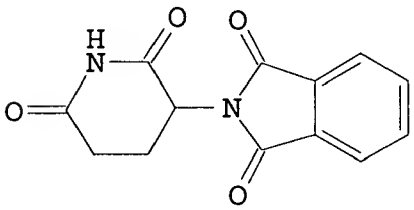
IT 50-35-1
RL: BIOL (Biological study)
(tumor cell attachment inhibition by, spontaneous decompn. products in relation to)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



IT 26581-81-7
RL: BIOL (Biological study)
(tumor cell attachment inhibition by, thalidomide in relation to)
RN 26581-81-7 HCAPLUS
CN 2,6-Piperidinedione, 3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



L84 ANSWER 53 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1984:543568 HCAPLUS
DOCUMENT NUMBER: 101:143568
TITLE: Teratogen metabolism: spontaneous decay hydrolysis products of thalidomide and thalidomide analog are not activated by liver microsomes
AUTHOR(S): Braun, A. G.; Weinreb, S. L.
CORPORATE SOURCE: Dep. Radiat. Ther., Harvard Med. Sch., Boston, MA, USA
SOURCE: Report (1983), DOE/ER/60070-T3; Order No. DE84006117, 18 pp. Avail.: NTIS
From: Energy Res. Abstr. 1984, 9(9), Abstr. No. 17444
DOCUMENT TYPE: Report
LANGUAGE: English
GI



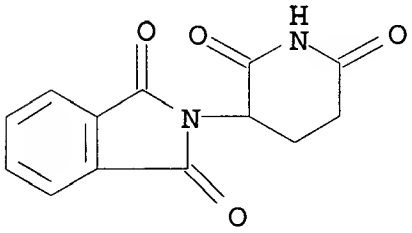
I

AB Thalidomide (I) [50-35-1] and 2 analogs, EM 87 [49785-74-2] and EM 12 [26581-81-7], inhibit the attachment of tumor cells to concanavalin A-coated surfaces only if the drugs are treated with hepatic microsomes and cofactors. Preincubation of these drugs in buffered saline at

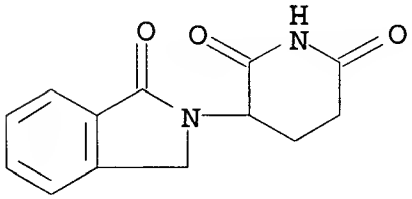
37.degree. results in a progressive decline in their ability to be activated to inhibitory products. Similarly, postincubation of the inhibitory products leads to a decline in their ability to inhibit attachment. Decay rates differ for the 3 compds. I, EM 87, and EM 12 require 3, 1, and 6 h, resp., to decline to control levels. These relative rates of decay are consistent with the relative teratogenicity of the 3 drugs.

IT 50-35-1 26581-81-7
RL: PROC (Process)
(activation of, by liver microsomes)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

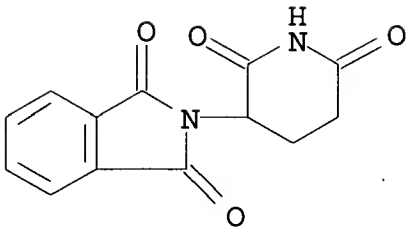


RN 26581-81-7 HCAPLUS
CN 2,6-Piperidinedione, 3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



IT 50-35-1D, hydrolysis products
RL: BIOL (Biological study)
(liver microsomes effect on)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



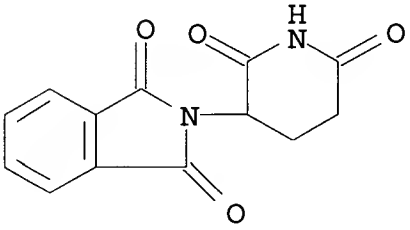
L84 ANSWER 54 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1984:503515 HCAPLUS
DOCUMENT NUMBER: 101:103515
TITLE: Teratogen metabolism: activation of thalidomide and thalidomide analogs to products that inhibit the attachment of cells to concanavalin A coated plastic surfaces
AUTHOR(S): Braun, Andrew G.; Weinreb, Steven L.
CORPORATE SOURCE: Dep. Radiat. Ther., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Biochem. Pharmacol. (1984), 33(9), 1471-7
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thalidomide (I) [50-35-1] metabolites inhibited the attachment of tumor cells to concanavalin A [11028-71-0]-coated polyethylene surfaces. I, itself, was noninhibitory. I activation to inhibitory products required hepatic microsomes, an NADPH-generating system, and O. Prodn. of inhibitory metabolites was unaffected by either epoxide hydrolase or 1,2-epoxy-3,3,3-trichloropropane, an inhibitor of epoxide hydrolase endogenous to hepatic S9 fraction. Therefore, the attachment inhibitor was probably not an arene oxide. Inhibition was not accompanied by cytotoxicity, as judged by trypan blue exclusion. Although uninduced hepatic microsomes from mice, rats, and dogs had similar abilities to activate I, microsomes from Aroclor 1254-induced rats were relatively inactive in the system. Inhibitory metabolites were generated from the I analogs EM8 [16477-31-9], EM12 [26581-81-7], EM16 [26581-91-9], EM87 [49785-74-2], EM136 [42472-96-8], EM255 [79458-80-3], E350 [303-31-1], phthalimide [85-41-6], phthalimidophthalimide [4388-29-8], indan [496-11-7], 1-indanone [83-33-0] and 1,3-indandione [606-23-5]. Glutarimide [1121-89-7], glutamic acid [56-86-0], and phthalic

acid [88-99-3] did not activate to inhibitory products.

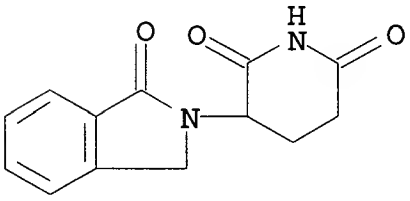
IT 50-35-1D, metabolites
RL: FORM (Formation, nonpreparative)
(formation of, by liver microsomes, tumor cell attachment to concanavalin A in relation to)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

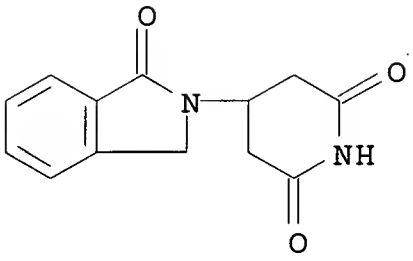


IT 26581-81-7 26581-91-9 42472-96-8
79458-80-3
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, by liver microsomes, tumor cell attachment to concanavalin A in relation to)

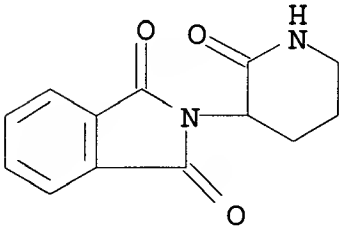
RN 26581-81-7 HCAPLUS
CN 2,6-Piperidinedione, 3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



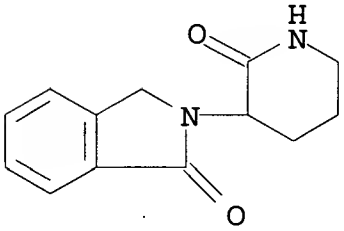
RN 26581-91-9 HCAPLUS
CN 2,6-Piperidinedione, 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



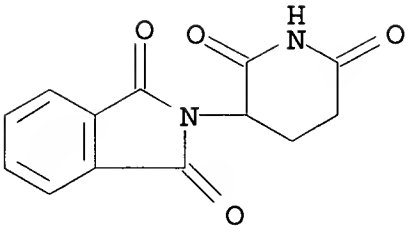
RN 42472-96-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2-oxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



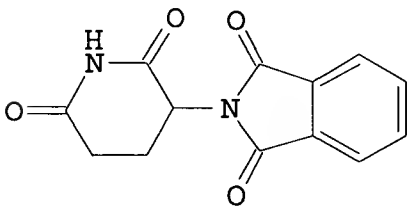
RN 79458-80-3 HCAPLUS
CN 1H-Isoindol-1-one, 2,3-dihydro-2-(2-oxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



IT 50-35-1
RL: BIOL (Biological study)
(tumor cell attachment to concanavalin A response to, analog metabolites in relation to)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 55 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1984:483948 HCAPLUS
DOCUMENT NUMBER: 101:83948
TITLE: Teratogen metabolism: activation of thalidomide and thalidomide analogs to products that inhibit the attachment of cells to concanavalin A coated plastic surfaces. Revised version
AUTHOR(S): Weinreb, S. L.
CORPORATE SOURCE: Dep. Radiat. Ther., Harvard Med. Sch., Boston, MA, USA
SOURCE: Report (1982), DOE/ER/60070-T1; Order NO. DE84006118, 32 pp. Avail.: NTIS
From: Energy Res. Abstr. 1984, 9(8), Abstr. No. 15071
DOCUMENT TYPE: Report
LANGUAGE: English
GI



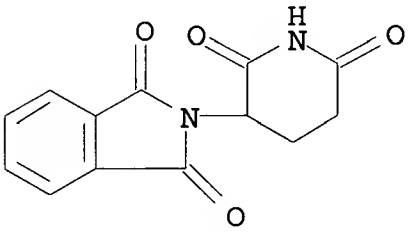
I

AB Thalidomide (I) [50-35-1] metabolites inhibit the attachment of tumor cells to concanavalin A-coated polyethylene surfaces. I itself is noninhibitory. I activation to inhibitory products requires hepatic microsomes, an NADPH generating

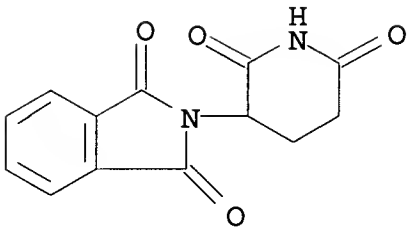
system and mol. O. Prodn. of inhibitory metabolites is unaffected by either epoxide hydrolase or TCPO, an inhibitor of epoxide hydrolase endogenous to hepatic S9 fraction. Therefore, the attachment inhibitor is probably not an arene oxide. Inhibition is not accompanied by cytotoxicity as judged by trypan blue exclusion. Although uninduced hepatic microsomes from mice, rats, and dogs have similar ability to activate I microsomes from Aroclor 1254 induced rats are relatively inactive in the system. Inhibitory metabolites can be generated from the I analogs EM8 [16477-31-9], EM12 [26581-81-7], EM16 [26581-91-9], EM87 [49785-74-2], EM136 [42472-96-8], EM255 [79458-80-3], E350 [303-31-1], phthalimide [85-41-6] phthalimido-phthalimide [4388-29-8] indan [496-11-7], 1-indanone [83-33-0], and 1,3-indandione [606-23-5]. Glutarimide [1121-89-7], glutamic acid [56-86-0] and phthalic acid [88-99-3] do not activate to inhibitory products.

IT 50-35-1 50-35-1D, metabolites
RL: BIOL (Biological study)
(neoplasm cell binding to concanavalin A-coated plastic surface response to)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

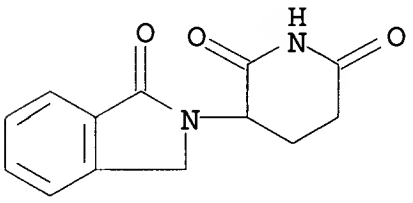


RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

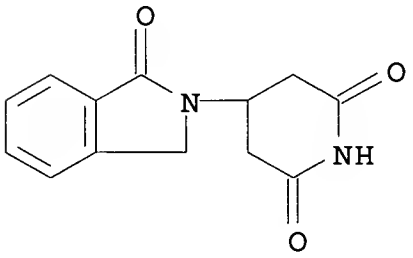


IT 26581-81-7 26581-91-9 42472-96-8
79458-80-3
RL: BIOL (Biological study)
(thalidomide effect on neoplasm cell attachment to concanavalin A-coated plastic surface response to)

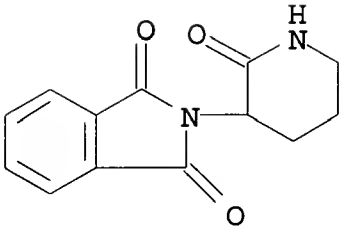
RN 26581-81-7 HCAPLUS
CN 2,6-Piperidinedione, 3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



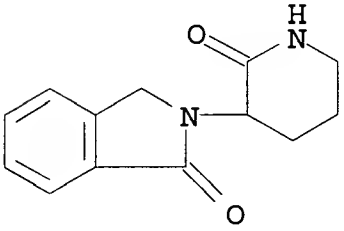
RN 26581-91-9 HCAPLUS
CN 2,6-Piperidinedione, 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



RN 42472-96-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2-oxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 79458-80-3 HCAPLUS
CN 1H-Isoindol-1-one, 2,3-dihydro-2-(2-oxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

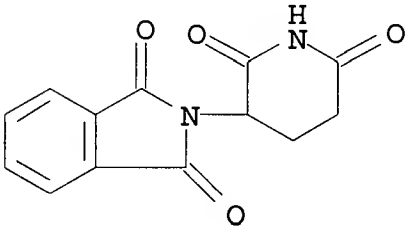


L84 ANSWER 56 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1983:589270 HCAPLUS
DOCUMENT NUMBER: 99:189270
TITLE: Screening for cytotoxicity in neuroblastoma cells. I. Dependence of growth inhibition on the presence of serum
AUTHOR(S): Mummery, C. L.; Van Den Brink, S.; Van Der Saag, P. T.; De Laat, S. W.
CORPORATE SOURCE: Hubrecht Lab., Int. Embryol. Inst., Utrecht, 3584 CT, Neth.
SOURCE: Toxicol. Lett. (1983), 18(3), 201-9
CODEN: TOLED5; ISSN: 0378-4274
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The growth-inhibitory effects of a variety of potentially toxic compds. on neuroblastoma cells in defined, serum-free medium were compared with those in serum-contg. medium. For 13 of 21 compds. tested, concns. between 2 and 105 times higher were required for 50% inhibition of growth in serum-contg. medium. The

ranking of substances for their potency in inhibiting growth was thereby different in the 2 different culture conditions. The presence of bovine serum albumin in the medium had similar effects on the dose-response curves.

IT 50-35-1
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of, to neuroblastoma cell, serum in relation to)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

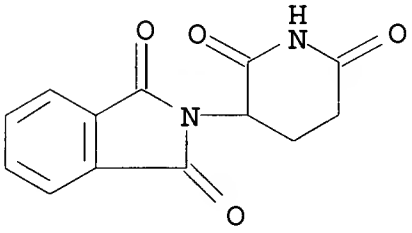


L84 ANSWER 57 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1982:175852 HCAPLUS
DOCUMENT NUMBER: 96:175852
TITLE: Quantitative correspondence between the in vivo and in vitro activity of teratogenic agents
AUTHOR(S): Braun, Andrew G.; Buckner, Christine A.; Emerson, David J.; Nichinson, Bradley B.
CORPORATE SOURCE: Dep. Radiat. Ther., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1982), 79(6), 2056-60
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

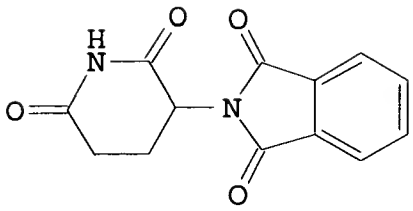
AB Seventy-four teratogenic and 28 nonteratogenic agents were tested in a developed in vitro teratogen assay. The assay identified teratogens by their ability to inhibit attachment of ascites tumor cells to plastic surfaces coated with concanavalin A. There was a qual. agreement between in vivo animal data and in vitro activity for 81 of 102 agents (79%). Quant. anal. showed a highly

significant correlation coeff. of 0.69 between the inhibitory in vitro dose and the lowest reported teratogenic dose for 54 of 60 inhibitory teratogens. The doses analyzed ranged over 5 orders of magnitude. These results were interpreted to mean that attachment inhibition in concert with other, complementary, in vitro assay systems can become a useful method for the assessment of the teratogenic potential of environmental agents.

IT 50-35-1
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(teratogenicity of)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 58 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1981:132131 HCAPLUS
DOCUMENT NUMBER: 94:132131
TITLE: Thalidomide metabolite inhibits tumor cell attachment to concanavalin A-coated surfaces
AUTHOR(S): Braun, Andrew G.; Dailey, James P.
CORPORATE SOURCE: Dep. Radiat. Therapy, Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Biochem. Biophys. Res. Commun. (1981), 98(4), 1029-34
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



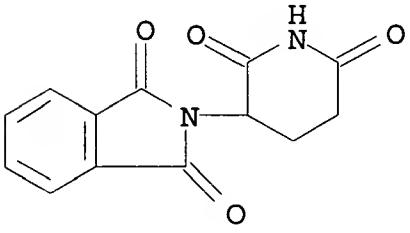
I

AB The inhibitory effect of drug treatment on tumor cell attachment to plastic surfaces coated with concanavalin A [11028-71-0] correlated well with the in vivo teratogenicity of the drug. The effects of thalidomide (I) [50-35-1] and some of its metabolites were examd. for inhibitory activity. While I and its hydrolysis products did not alter attachment, metabolites of I produced by incubation of the drug with murine liver microsomes were inhibitory. Generation of inhibitory products required the presence of glucose-6-phosphate, NADP, glucose-6-phosphate dehydrogenase, and MgCl2. The degree of inhibition was dependent on the duration of incubation at 37.degree.. These results suggest a model for the teratogenic action of I in which metabolites of the drug alter cell surface function leading to interference with normal morphogenic cell to cell interactions.

IT 50-35-1D, metabolite
RL: BIOL (Biological study)
(neoplasm cell attachment to concanavalin A-coated plastic surface inhibition by, as teratogenesis study model)

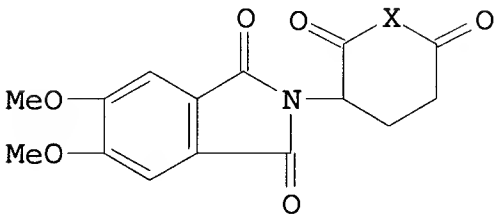
RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

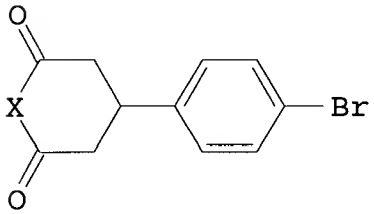


L84 ANSWER 59 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1978:579814 HCAPLUS
DOCUMENT NUMBER: 89:179814
TITLE: Possible antineoplastic agents: part IV. Synthesis and antineoplastic potency of N-substituted .alpha.-(4,5-dimethoxyphthalimido)glutarimides and N-substituted .beta.-(4-bromophenyl)glutarimides
AUTHOR(S): De, A. U.; Ghose, A. K.
CORPORATE SOURCE: Dep. Pharm., Jadavpur Univ., Calcutta, India
SOURCE: Indian J. Chem., Sect. B (1978), 16B(6), 510-12
CODEN: IJSBDB; ISSN: 0376-4699
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, X=NR
III, X=O



II, X=NR
IV, X=O

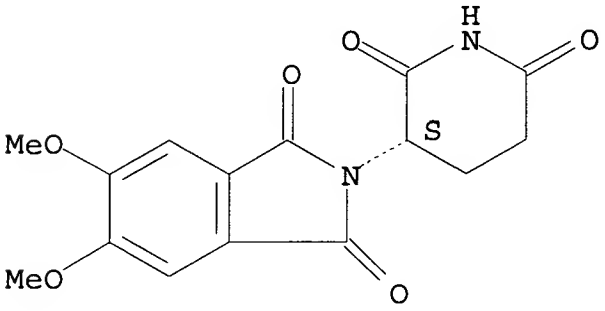
AB .alpha.-(4,5-Dimethoxyphthalimido)glutarimides I and .beta.-(4-bromophenyl)glutarimides II (R = H, alkyl, cyclohexyl, Ph, PhCH2) were prepd. by treating III and IV with RNH2 and tested in Ehrlich Ascites carcinoma in Swiss albino mice. Some I possess significant anticancer activity at a dose level of 50 mg/kg i.p.

IT 68030-92-2P 68030-94-4P 68030-95-5P
68030-96-6P 68030-97-7P 68030-98-8P
RL: BAC (Biological activity or effector, except adverse); SPN

(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antineoplastic activity of)

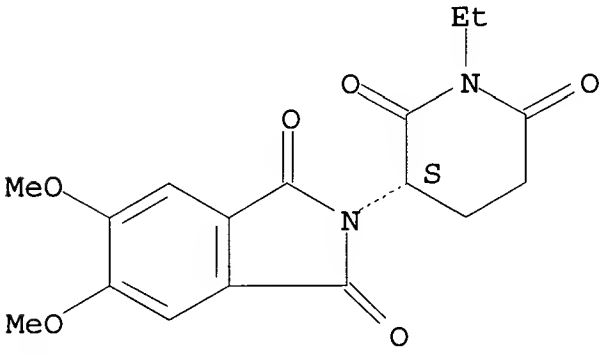
RN 68030-92-2 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



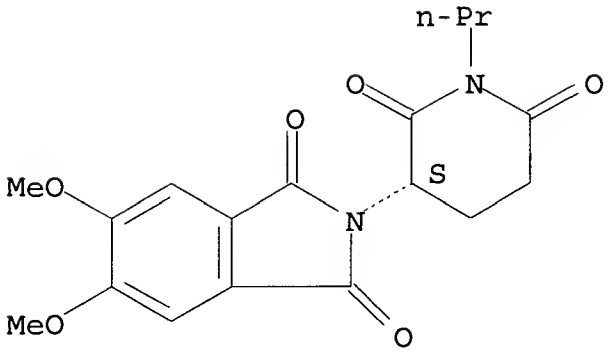
RN 68030-94-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-ethyl-2,6-dioxo-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



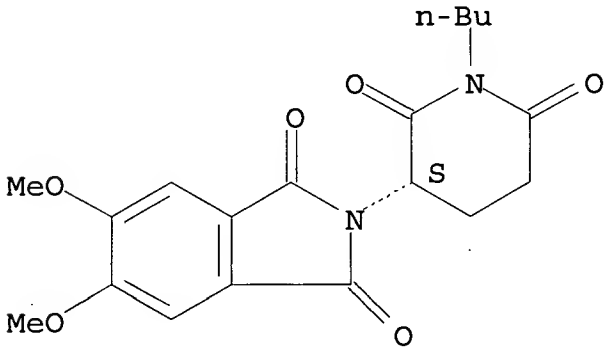
RN 68030-95-5 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-propyl-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



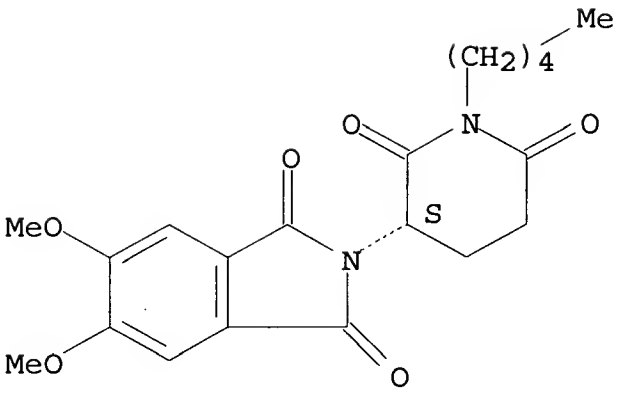
RN 68030-96-6 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-butyl-2,6-dioxo-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



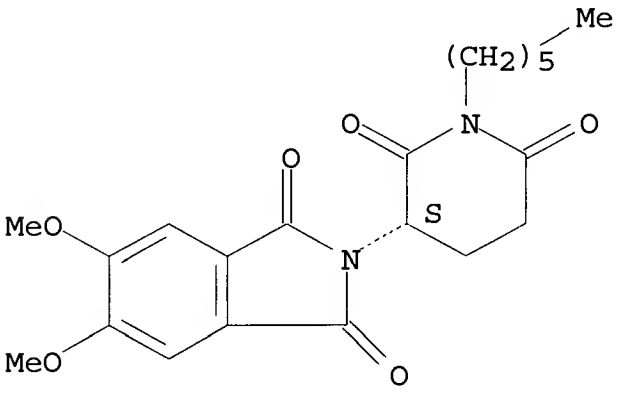
RN 68030-97-7 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-pentyl-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



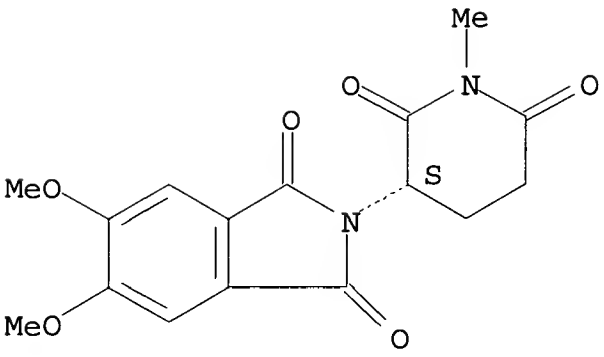
RN 68030-98-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-hexyl-2,6-dioxo-3-piperidinyl)-5,6-dimethoxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 68030-93-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and oxidn. of)
RN 68030-93-3 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5,6-dimethoxy-2-(1-methyl-2,6-dioxo-3-piperidinyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L84 ANSWER 60 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1978:523283 HCAPLUS

DOCUMENT NUMBER: 89:123283

TITLE: Significance of neutrophil activation in reactional lepromatous leprosy: effects of thalidomide in vivo and in vitro. Activation in adjuvant disease

AUTHOR(S): Goihman-Yahr, Mauricio; Convit, Jacinto; Rodriguez-Ochoa, Gilberto; Aranzazu, Nacarid; Villalba-Pimentel, Luis; Ocanto, Ana; De Gomez, Maria Elena

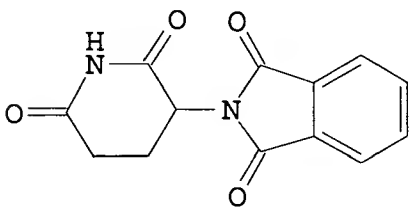
CORPORATE SOURCE: Inst. Nac. Dermatol., Univ. Cent. Venezuela, Caracas, Venez.

SOURCE: Int. Arch. Allergy Appl. Immunol. (1978), 57(4), 317-32
CODEN: IAAAAM; ISSN: 0020-5915

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



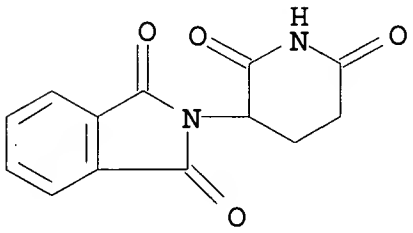
I

AB Thalidomide (I) [50-35-1] produced clin. improvement in patients with reactional lepromatous leprosy before a decrease in neutrophils forming formazan ppts. (FP cells). Concomitant infectious processes induced FP cell activation even in patients treated with I. In vitro, I did not affect spontaneous redn. of nitroblue tetrazolium by neutrophils, nor did it block endotoxin-induced activation. Thus, the therapeutic effect of I is not related to inhibition of neutrophil activation. In rats, from a strain refractory to adjuvant disease, injected with mycobacteria, no adjuvant disease or neutrophil activation were obsd.; whereas, in rats susceptible to adjuvant disease, an increase in FP cells was obsd. shortly after injection of mycobacteria, but before the onset of adjuvant disease. Thus, tissue damage in reactional lepromatous leprosy is not due solely to neutrophil action by a mechanism similar to that of immune complex disease.

IT 50-35-1
RL: BIOL (Biological study)
(leprosy response to, neutrophil activation in)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 61 OF 71 HCAPLUS COPYRIGHT 1996 ACS

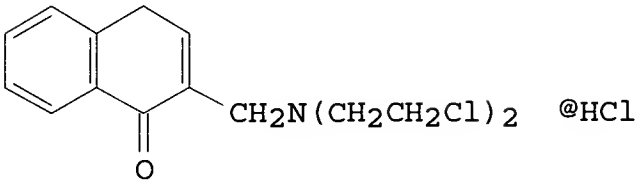
ACCESSION NUMBER: 1977:545546 HCAPLUS

DOCUMENT NUMBER: 87:145546

TITLE: Structure-effect interactions in Mannich bases with and without nitrogen-mustard groups andsome reduction products derived from .beta.-aminoketones on the basis of a cancerostatic-3-step testwith transplantation tumors

AUTHOR(S): Werner, W.; Jungstand, W.; Gutsche, W.;

Wohlrabe, K.
CORPORATE SOURCE: Forschungszent. Molekularbiol. Med., DAW, Jena, E. Ger.
SOURCE: Pharmazie (1977), 32(6), 341-7
CODEN: PHARAT
DOCUMENT TYPE: Journal
LANGUAGE: German
GI



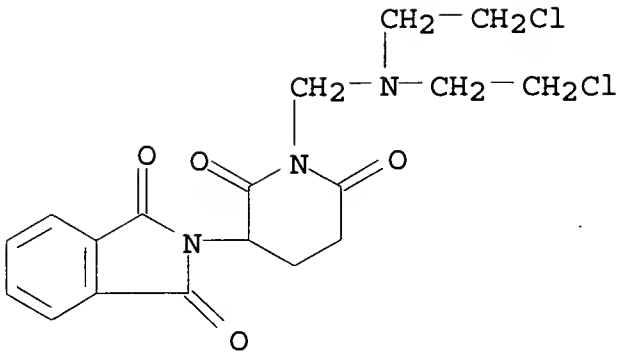
I

AB The effects of 68 Mannich bases and 16 comparison compds. on transplanted tumors (Ehrlich ascites carcinoma, leukemia L 1210, myeloid leukema, Crocker sarcoma, and Walker carcinosarcoma) were studied by a 3-step method. One of 7 C-Mannich bases with aliph. nitrogen mustard groups (which rapidly cleaved Cl), 2-[bis-(2-chloroethyl)aminomethyl]-benzocyclohexen-1-one-HCl (I) [17797-98-7], inhibited Crocker Sarcoma in mice by 50% at 8.0 mg/kg. The 17 C-Mannich bases with arom. nitrogen mustard groups (slowly cleaved Cl) did not inhibit tumor growth. Several derivs. of this type activated by redn. of the carbonyl groups were cancerostatic for Walker carcinosarcoma. Eleven monovalent and 3 di or trivalent .beta.-amino ketones and 17 N-Mannich bases (C-Mannich bases without nitrogen mustard groups) (mono- or divalent aminomethyl compds.) had no effect on tumor growth. However, 9 of 13 N-Mannich bases with nitrogen mustard groups as amine components had strong reproducible cancerostatic effects, esp. against myeloid leukemia and Walker carcinosarcoma.

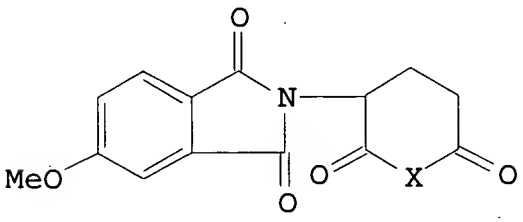
IT 23192-96-3
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by)

RN 23192-96-3 HCAPLUS

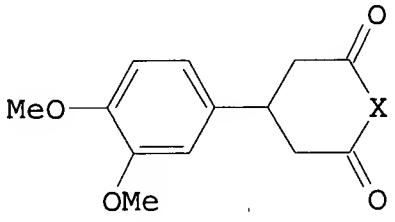
CN 1H-Isoindole-1,3(2H)-dione, 2-[1-[[bis(2-chloroethyl)amino]methyl]-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)



L84 ANSWER 62 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1977:534378 HCAPLUS
DOCUMENT NUMBER: 87:134378
TITLE: Possible antineoplastic agents. III. Synthesis of 6-alkyl-2-[4'-methoxyphthalimido] and 6-alkyl-3-[3'-4'-dimethoxyphenyl]glutarimides
AUTHOR(S): De, A. U.; Ghose, A. K.
CORPORATE SOURCE: Dep. Pharm., Jadavpur Univ., Calcutta, India
SOURCE: J. Indian Chem. Soc. (1976), 53(11), 1122-5
CODEN: JICSAH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, X=NR
II, X=O



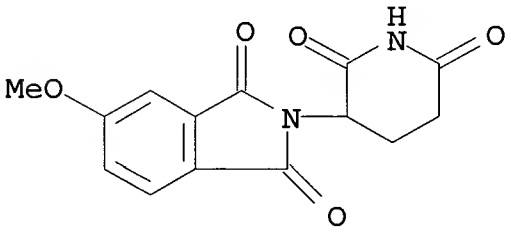
III, X=NR
IV, X=O

AB The .alpha.-phthalimidoglutarimides I [R = H, Me, Ph, PhCH2, cyclohexyl, Me(CH2)n (n = 1-5)] were prepd. by treating

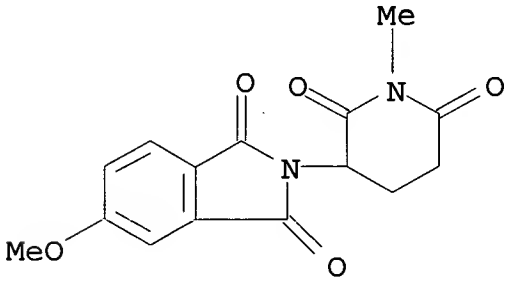
4-methoxyphthalic anhydride with HO2CCH(NH2)CH2CH2CO2H followed by cyclization to give II, which was treated with RNH2. The phenylglutarimides III [R = H, Me, Ph, PhCH2, cyclohexyl, Me(CH2)n (n = 1-5)] were prepd. by condensation of 3,4-(MeO)2C6H3CHO with 2 moles MeCOCH2CO2Et followed by hydrolysis and cyclization to give IV, which was treated with RNH2. At 50 mg/kg I (R = Et) inhibited Ehrlich ascites carcinoma in mice by 70.52%.

IT 64139-03-3P 64139-04-4P 64139-05-5P
64139-06-6P 64139-07-7P 64139-08-8P
64139-09-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antineoplastic activity of)

RN 64139-03-3 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)

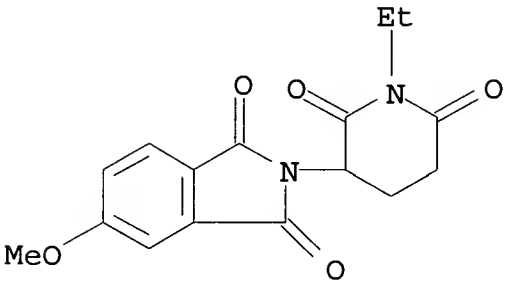


RN 64139-04-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-methoxy-2-(1-methyl-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



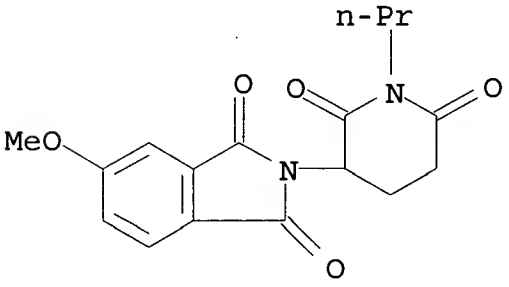
RN 64139-05-5 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(1-ethyl-2,6-dioxo-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)



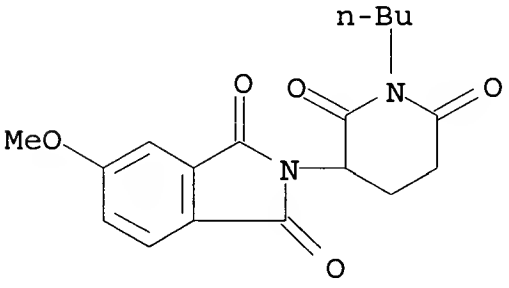
RN 64139-06-6 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-propyl-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)

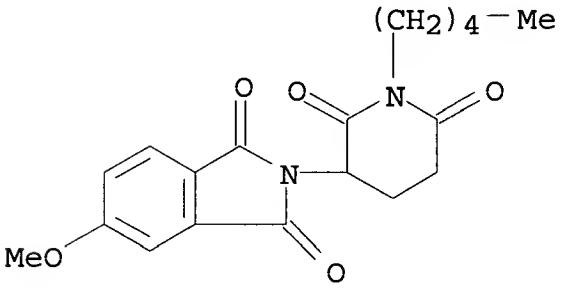


RN 64139-07-7 HCAPLUS

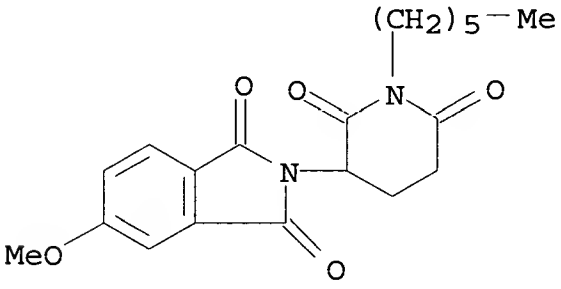
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-butyl-2,6-dioxo-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)



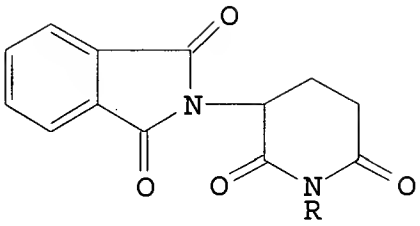
RN 64139-08-8 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-pentyl-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)



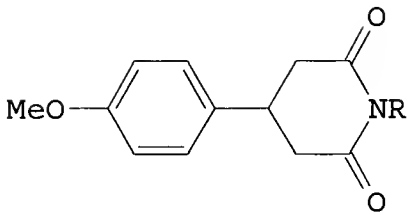
RN 64139-09-9 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-hexyl-2,6-dioxo-3-piperidinyl)-5-methoxy- (9CI) (CA INDEX NAME)



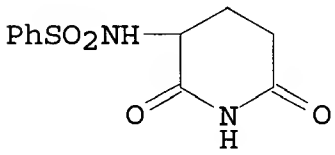
L84 ANSWER 63 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1977:170837 HCAPLUS
DOCUMENT NUMBER: 86:170837
TITLE: Possible antineoplastic agents. II
AUTHOR(S): De, A. U.; Pal, D.
CORPORATE SOURCE: Dep. Pharm., Jadavpur Univ., Calcutta, India
SOURCE: J. Pharm. Sci. (1977), 66(2), 232-5
CODEN: JPMSAE
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



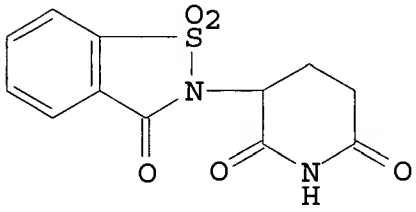
I



II



III



IV

AB Various glutarimide derivs., e.g. I (R = Ph, cyclohexyl, PhCH2), II (R = Me, Et, Pr) III, and IV, were synthesized, and some showed significant activity against Ehrlich ascites carcinoma in Swiss albino mice. Thus, 3-(p-methoxyphenyl)glutaric anhydride was treated with MeNH2 to give II (R = Me). I (R = Ph) inhibited ascitic cells by 87.31% in mice.

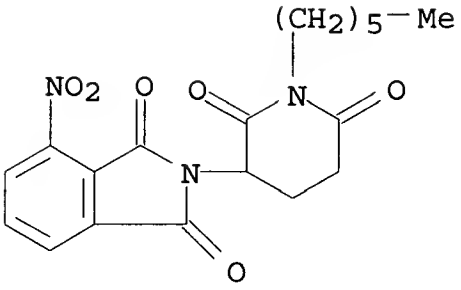
IT 62595-73-7P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

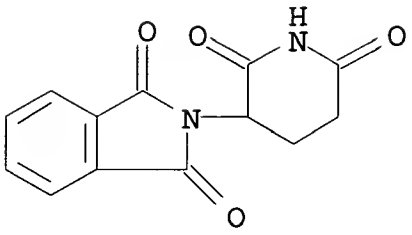
(prepn. and antineoplastic activity of)

RN 62595-73-7 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(1-hexyl-2,6-dioxo-3-piperidinyl)-4-nitro- (9CI) (CA INDEX NAME)

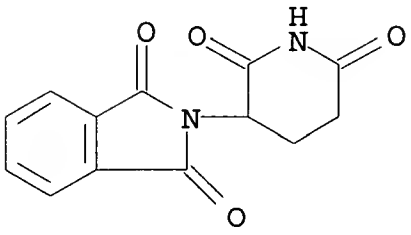


L84 ANSWER 64 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1977:165077 HCAPLUS
DOCUMENT NUMBER: 86:165077
TITLE: Quantitative structure-activity relation (QSAR) and rational drug design for some antineoplastic thalidomide and glutarimide derivatives
AUTHOR(S): De, A. U.; Pal, D.
CORPORATE SOURCE: Dep. Pharm., Jadavpur Univ., Calcutta, India
SOURCE: J. Indian Chem. Soc. (1976), 53(10), 1049-52
CODEN: JICSAH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Quant. structure-activity relationship (QSAR) of 38 thalidomide and glutarimide derivs. I, evaluated as possible antineoplastic agents against Ehrlich ascites carcinoma, has been detd. with the help of the Free-Wilson model which results in the prediction and rational designing of the most potent member in this class of compds.
IT 50-35-1D, derivs.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibiting activity of, evaluation of)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

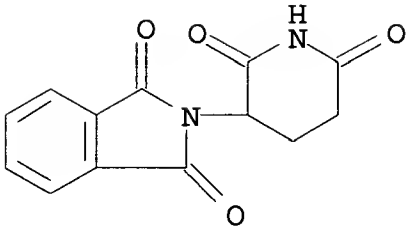


L84 ANSWER 65 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1976:537359 HCAPLUS
DOCUMENT NUMBER: 85:137359
TITLE: Factors related to tumor spread in the body
AUTHOR(S): Boggust, W. A.
CORPORATE SOURCE: Dep. Exp. Med., Trinity Coll., Dublin, Ire.
SOURCE: Adv. Tumour Prev., Detect. Charact. (1976), 3(Biol. Charact. Hum. Tumours, Proc. Int. Symp., 6th, 1975), 383-90
CODEN: APDCDT
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB In exts. of human cancers, cathepsins B, C, and D, leucine aminopeptidase [9001-61-0], glucosaminidase [9027-56-9], acid and neutral collagenase [9001-12-1], and fibrinolysin [9001-90-5] activities were found. Collagenase was blocked by the chelating agents dimercaptopropanol (BAL) [59-52-9], EDTA [60-00-4], and o-phenanthroline (I) [66-71-7], and the cytostatic drug ICRF-159 (II) [21416-87-5]. Combinations of I and II were synergistic. II also inhibited cathepsins C and B1 and probably glucosaminidase, but not cathepsin D or leucineaminopeptidase. Mice bearing implanted carcinoma excised on the 10th day, died from lung metastases within 34 days unless otherwise treated. Survival periods were increased by II, but not by I alone. Combinations of I and II substantially increased the survival period. Thus, I and II by acting as enzyme inhibitors and cytotoxic agents they helped to inhibit primary tumor growth and prevent metastases.
IT 50-35-1
RL: BIOL (Biological study)
(enzymes inhibition by, in neoplasm)
RN 50-35-1 HCAPLUS

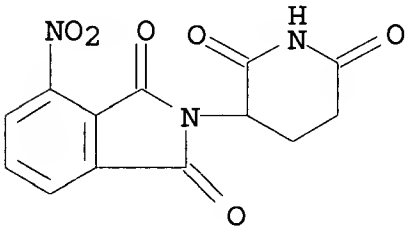
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



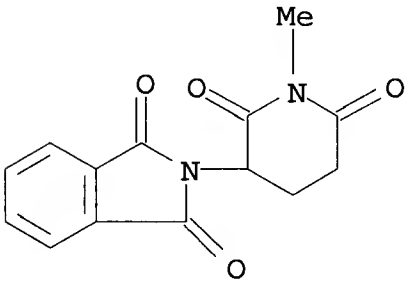
L84 ANSWER 66 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1975:149307 HCAPLUS
DOCUMENT NUMBER: 82:149307
TITLE: Possible antineoplastic agents. I
AUTHOR(S): De, A. U.; Pal, D.
CORPORATE SOURCE: Dep. Pharm., Jadavpur Univ., Calcutta, India
SOURCE: J. Pharm. Sci. (1975), 64(2), 262-6
CODEN: JPMSAE
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Most of the 9 thalidomide derivs., such as 6-n-hexyl-2-phthalimidoglutarimide (I) [54946-25-7], and the 8 glutarimide derivs., such as 6-methyl-3-phenylglutarimide (II) [54946-26-8], which were synthesized had good antineoplastic activity against Ehrlich ascites carcinoma in mice.
IT 50-35-1P 19171-18-7P 42472-93-5P
54946-21-3P 54946-22-4P 54946-23-5P
54946-24-6P 54946-25-7P 55003-81-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and neoplasm inhibitory activity of)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



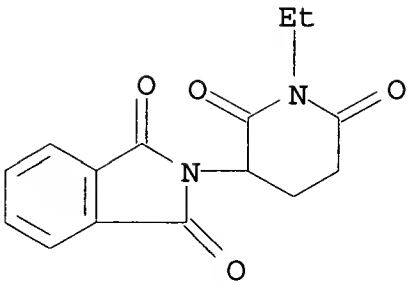
RN 19171-18-7 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-4-nitro-
(9CI) (CA INDEX NAME)



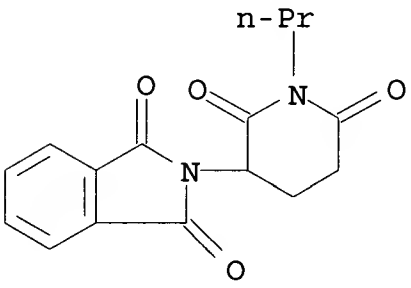
RN 42472-93-5 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-methyl-2,6-dioxo-3-piperidinyl)-
(9CI) (CA INDEX NAME)



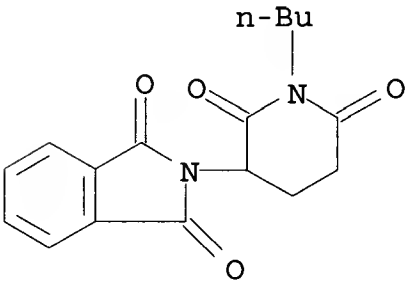
RN 54946-21-3 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-ethyl-2,6-dioxo-3-piperidinyl)-
(9CI) (CA INDEX NAME)



RN 54946-22-4 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-propyl-3-piperidinyl)-
(9CI) (CA INDEX NAME)

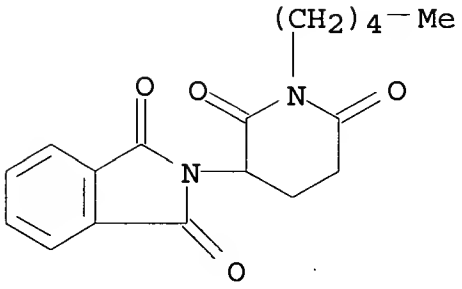


RN 54946-23-5 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-butyl-2,6-dioxo-3-piperidinyl)-
(9CI) (CA INDEX NAME)

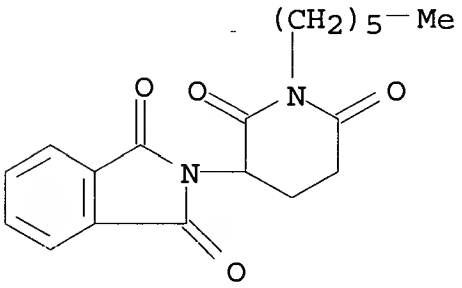


RN 54946-24-6 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-1-pentyl-3-piperidinyl)-

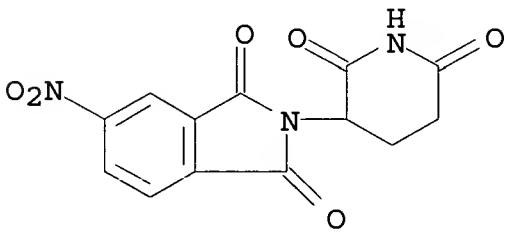
(9CI) (CA INDEX NAME)



RN 54946-25-7 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(1-hexyl-2,6-dioxo-3-piperidinyl)-
(9CI) (CA INDEX NAME)

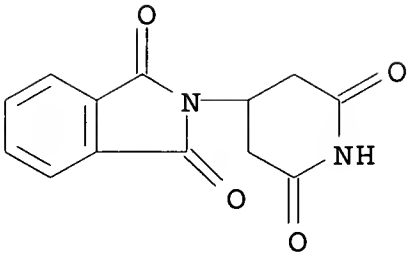


RN 55003-81-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-5-nitro-
(9CI) (CA INDEX NAME)



L84 ANSWER 67 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1975:68668 HCAPLUS
DOCUMENT NUMBER: 82:68668
TITLE: Effects of 2-bromine- .alpha.-ergocryptine, L-dopa, and cyclic imides on serum prolactin in postmenopausal women
AUTHOR(S): Rozencweig, M.; Heuson, J. C.; Bila, S.; L'Hermite, M.; Robyn, C.
CORPORATE SOURCE: Cent. Tumeurs, Univ. Libre Bruxelles, Brussels, Belg.
SOURCE: Eur. J. Cancer (1973), 9(9), 657-64
CODEN: EJCAAH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB A single dose of 500 mg L-dopa or 5 mg CB 154 (2-bromo-.alpha.-ergocryptine) (I) [25614-03-3] significantly decreased serum prolactin levels in postmenopausal women, whereas the cyclic imide derivs., CG 809 (4-phthalimido-2,6-piperidinedione) [303-31-1] and CG 603 [1-(morpholinomethyl)-4-phthalimido-2,6-piperidinedione] [10329-96-1] had no influence on prolactin levels. During chronic L-dopa treatment (500 mg every 6 hr), the high broad peaks occurring during the night in the curves representing the pretreatment circadian rhythm of serum prolactin levels became saw-toothed with short-lasting falls after each dose followed by sharp rebounds. I (5 mg 3 times daily) induced a profound and sustained decrease in prolactin levels, completely abolishing the circadian rhythm. I is a more effective prolactin-inhibiting agent than L-dopa although neither compd. achieved complete suppression. Potential value of prolactin inhibitors in treatment of breast cancer and other neoplasms was discussed.
IT 303-31-1
RL: BIOL (Biological study)
(prolactin secretion inhibition by, after menopause)
RN 303-31-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-4-piperidinyl)- (9CI) (CA INDEX NAME)

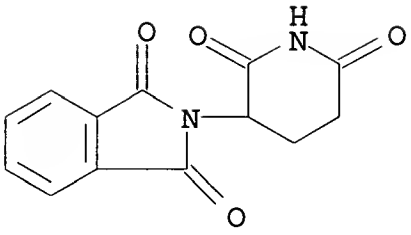


L84 ANSWER 68 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1972:497723 HCAPLUS
DOCUMENT NUMBER: 77:97723
TITLE: Use of chemosterilants for insect control and the research carried out in this area in the Czechoslovak Socialist Republic
AUTHOR(S): Landa, Vladimir; Rezabova, Blanka
CORPORATE SOURCE: Entomol. Ustav, Cesk. Akad. Ved, Prague, Czech.
SOURCE: Tagungsber., Deut. Akad. Landwirtschaftswiss. Berlin (1969), No. 80(Pt. 1), 101-4
CODEN: TDLBAI
DOCUMENT TYPE: Journal
LANGUAGE: German

AB Application of cytostatic agents, e.g. 6-azauridine (I) [54-25-1], aminopterin [54-62-6], or thio-TEPA [52-24-4], to Musca domestica resulted in formation of follicular cell tumors which orginated at the lower pole of the egg chamber, grew to fill the egg chamber, then degenerated and were resorbed together with the entire egg chamber. Thalidomide [50-35-1], in contrast, interrupted egg chamber development before or at the beginning of yolk formation without causing proliferation.

IT 50-35-1
RL: BIOL (Biological study)
(as insect sterilant)

RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



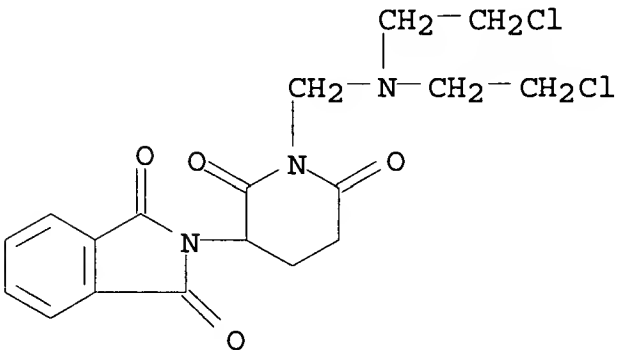
L84 ANSWER 69 OF 71 HCAPLUS COPYRIGHT 1996 ACS
ACCESSION NUMBER: 1971:139132 HCAPLUS
DOCUMENT NUMBER: 74:139132
TITLE: Three step test for screening potential cancerostatics. 1. Screening program and results of the first step
AUTHOR(S): Jungstand, W.; Gutsche, W.; Wohlrabe, K.
CORPORATE SOURCE: Inst. Mikrobiol. Exp. Ther., Dtsch. Akad. Wiss. Berlin, Jena, Ger.
SOURCE: Arzneim.-Forsch. (1971), 21(3), 404-10
CODEN: ARZNAD
DOCUMENT TYPE: Journal
LANGUAGE: German
GI For diagram(s), see printed CA Issue.
AB The 3-step test proposed for screening potential cancerostatics included: step 1, tests against a hyperdiploid Ehrlich ascites carcinoma, an immature cell leukemic myelosis, and a hyperdiploid sarcoma 180 in mice; step 2, dose-effect curves and therapeutic index detn.; step 3, further testing against other tumors and detn. of side effects. Results of the 1st step with 15 N mustard benzimidazoles, 16 azomethines with N mustard or bis(.beta.-hydroxyethyl)amino groups, 4 N mustard dicyanethylenes, 11 Mannich bases without N mustard groups, 11 Mannich bases with N mustard groups, 5 other N mustard compds., 5 bromobutyl ethers, 4 purine complexes, and 18 other compds. indicated that 38 were active against at least 1 tumor and should be further tested. Only (p-[bis(.beta.-chloroethyl)amino]phenylimino)cyanoacetic acid .beta.-hydroxyethylamide (I) was active against all 3 tumors. 1,2-Dimethyl-5-bis-(.beta.-chloroethyl)amino-7-azabenzimidazole-HCl, (p-[bis(.beta.-chloroethyl)amino]phenylimino)cyanoacetic acid N,N-dimethylhydrazide, 5-(p-[bis(.beta.-chloroethyl)amino]phenylimino)hydantoin, and 3-oxo-2-(p-[bis(.beta.-

chloroethyl)amino]phenylamino)-5,5-bis(hydroxymethyl)morpholone were relatively active against 2 of the tumors.

IT 23192-96-3
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(neoplasm inhibitor activity of)

RN 23192-96-3 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-[1-[[bis(2-chloroethyl)amino]methyl]-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)



L84 ANSWER 70 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1971:123495 HCAPLUS

DOCUMENT NUMBER: 74:123495

TITLE: Immunosuppressant action of thalidomide and prednisolone in rats with experimentally-induced neoplasia

AUTHOR(S): Guidetti, Ettore; Moiraghi-Ruggenini, A.; Errigo, E.; Martelli, M. P.

CORPORATE SOURCE: Ist. Ig., Univ. Torino, Turin, Italy

SOURCE: Cancro (1969), 22(5), 503-12
CODEN: CAROAF

DOCUMENT TYPE: Journal

LANGUAGE: Italian

GI For diagram(s), see printed CA Issue.

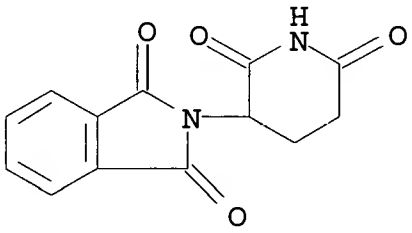
AB A particular test of complement activity elicited by reaction of serum factor with an RNA isolated from a mutant of S. cerevisiae was performed in order to analyze the activity of thalidomide (I) and prednisolone (II) as immunosuppressant drugs in rats. I or II were given i.p. to rats with a mean wt. of 140 g for 10 consecutive days at the resp. daily doses of 100 mg (as Na salt) and 10 mg. Half of

the rats were previously inoculated e.g. with 6 .times. 106 cells of Yoshida tumor. In all the control animals without tumor the production of the serum factor was not inhibited whereas increasing nos. of rats inoculated with tumor cells showed a deficiency of the factor (20% of the rats at the 1st day, 90% at the 5th, 100% at the 9th and 10th day). I and II were without effect in control rats whereas in rats inoculated with tumor cells an addnl. immunosuppressant action was evidenced (100% of the rats showed deficiency of the serum factor at the 5th day with I and at the 7th day with II). In .apprx.10% of the above rats the reaction for the serum factor turned pos. at the 7th-10th day with I but not with II.

IT 50-35-1
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of, in neoplasia)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 71 OF 71 HCAPLUS COPYRIGHT 1996 ACS

ACCESSION NUMBER: 1970:98435 HCAPLUS

DOCUMENT NUMBER: 72:98435

TITLE: Potentiating effect of thalidomide on methylcholanthrene oncogenesis in mice

AUTHOR(S): Miura, Mitsuhiko; Southam, Chester M.; Wuest, Heinz M.

CORPORATE SOURCE: Sloan Kettering Inst. for Cancer Res., New York, N. Y., USA

SOURCE: Experientia (1970), 26(3), 305-6
CODEN: EXPEAM

DOCUMENT TYPE: Journal

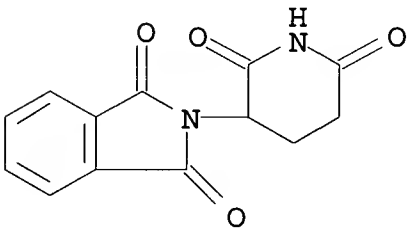
LANGUAGE: English

AB The i.p. administration of thalidomide (25 mg/day for 5 days in each of 4 consecutive weeks) to mice increased the no. of papillomas which developed in response to applications of methylcholanthrene (I) (0.2 ml of a 1% soln. for 5 consecutive days) to skin; thalidomide was started 1 week before I and was continued until 1 or 2 weeks after the application of I had stopped. There was no evidence that thalidomide enhanced I oncogenesis via immunosuppression. The oral administration of thalidomide at the same dosage and on the same schedule did not significantly increase the oncogenic response to I.

IT 50-35-1
RL: BIOL (Biological study)
(methylcholanthrene neoplasms induction potentiation by)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



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The prognostic significance of tumor vascularity in intermediate-thickness (0.76-4.0 mm thick) skin melanoma. A quantitative histologic study.

Srivastava A ; Laidler P; Davies RP; Horgan K; Hughes LE
Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff, United Kingdom.

Am J Pathol (UNITED STATES) Nov 1988 , 133 (2) p419-23, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 8902
Subfile: AIM; INDEX MEDICUS

The vascularity of 20 primary skin melanomas was assessed histologically. These cases were selected from patients with intermediate thickness melanomas (0.76-4.0 mm thick) treated surgically to provide two groups of ten patients. One group had no evidence of recurrence with a minimum follow-up of 9 years. The second group of ten patients developed locoregional or systemic metastasis under follow-up, and seven of these patients died of disseminated melanoma. Age, sex, Breslow's tumor thickness, and Clark's level of invasion were similar in the two groups. Vascular quantitation was carried out by image analysis after vascular definition by Ulex europaeus-I agglutinin staining. The percentage vascular area at the tumor base in the recurrence group was more than twice that in the recurrence-free group. This study suggests that increased vascularity at the tumor base may have prognostic significance in intermediate thickness melanomas.

Tags: Female; Human; Male; Support, Non-U.S. Gov't
Descriptors: *Melanoma--Blood Supply--BS; *Skin Neoplasms--Blood Supply --BS; Blood Vessels--Pathology--PA; Melanoma--Pathology--PA; Middle Age; Neoplasm Invasiveness; Prognosis; Skin Neoplasms--Pathology--PA